

## NEW COMPOUNDS

### FIELD OF THE INVENTION

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The present invention relates to new compounds of formula **Ia** and **Ib**, as a free base or a salt thereof, to pharmaceutical formulations containing said compounds and to the use of said compounds in therapy. The present invention further relates to processes for the preparation of compounds of formula **Ia** and **Ib** and to new intermediates used in the preparation thereof.

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### BACKGROUND OF THE INVENTION

15 Glycogen synthase kinase 3 (GSK3) is a serine / threonine protein kinase composed of two isoforms ( $\alpha$  and  $\beta$ ), which are encoded by distinct genes but are highly homologous within the catalytic domain. GSK3 is highly expressed in the central and peripheral nervous system. GSK3 phosphorylates several substrates including tau,  $\beta$ -catenin, glycogen synthase, pyruvate dehydrogenase and elongation initiation factor 2b (eIF2b). Insulin and growth factors activate protein kinase B, which phosphorylates GSK3 on serine 9 residue and inactivates it.

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#### *Alzheimer's Disease (AD) dementias, and tauopathies*

AD is characterized by cognitive decline, cholinergic dysfunction and neuronal death, neurofibrillary tangles and senile plaques consisting of amyloid- $\beta$  deposits. The sequence of these events in AD is unclear, but is believed to be related. Glycogen synthase kinase 3 $\beta$  (GSK3 $\beta$ ) or Tau ( $\tau$ ) phosphorylating kinase selectively phosphorylates the microtubule associated protein  $\tau$  in neurons at sites that are hyperphosphorylated in AD brains. Hyperphosphorylated protein  $\tau$  has lower affinity for microtubules and accumulates as paired helical filaments, which are the main components that constitute neurofibrillary tangles and neuropil threads in AD brains. This results in depolymerization of microtubules, which leads to dying back of axons and neuritic dystrophy. Neurofibrillary

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tangles are consistently found in diseases such as AD, amyotrophic lateral sclerosis, parkinsonism-dementia of Gaum, corticobasal degeneration, dementia pugilistica and head trauma, Down's syndrome, postencephalatic parkinsonism, progressive supranuclear palsy, Niemann-Pick's Disease and Pick's Disease. Addition of amyloid- $\beta$  to primary

5 hippocampal cultures results in hyperphosphorylation of  $\tau$  and a paired helical filaments-like state via induction of GSK3 $\beta$  activity, followed by disruption of axonal transport and neuronal death (Imahori and Uchida, J. Biochem 121:179-188, 1997). GSK3 $\beta$  preferentially labels neurofibrillary tangles and has been shown to be active in pre-tangle neurons in AD brains. GSK3 protein levels are also increased by 50% in brain tissue from

10 AD patients. Furthermore, GSK3 $\beta$  phosphorylates pyruvate dehydrogenase, a key enzyme in the glycolytic pathway and prevents the conversion of pyruvate to acetyl-Co-A (Hoshi et al., PNAS 93:2719-2723, 1996). Acetyl-Co-A is critical for the synthesis of acetylcholine, a neurotransmitter with cognitive functions. Thus, GSK3 $\beta$  inhibition may have beneficial effects in progression as well as the cognitive deficits associated with Alzheimer's disease

15 and other above-referred to diseases.

#### *Chronic and Acute Neurodegenerative Diseases*

Growth factor mediated activation of the PI3K /Akt pathway has been shown to play a key role in neuronal survival. The activation of this pathway results in GSK3 $\beta$  inhibition.

20 Recent studies (Bhat et. al., PNAS 97:11074-11079 (2000)) indicate that GSK3 $\beta$  activity is increased in cellular and animal models of neurodegeneration such as cerebral ischemia or after growth factor deprivation. For example, the active site phosphorylation was increased in neurons vulnerable to apoptosis, a type of cell death commonly thought to occur in chronic and acute degenerative diseases such as Alzheimer's Disease, Parkinson's Disease,

25 amyotrophic lateral sclerosis, Huntington's Disease and HIV dementia, ischemic stroke and head trauma. Lithium was neuroprotective in inhibiting apoptosis in cells and in the brain at doses that resulted in the inhibition of GSK3 $\beta$ . Thus GSK3 $\beta$  inhibitors could be useful in attenuating the course of neurodegenerative diseases.

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#### *Bipolar Disorders (BD)*

Bipolar Disorders are characterised by manic episodes and depressive episodes. Lithium has been used to treat BD based on its mood stabilising effects. The disadvantage of lithium is the narrow therapeutic window and the danger of overdosing that can lead to lithium intoxication. The recent discovery that lithium inhibits GSK3 at therapeutic concentrations has raised the possibility that this enzyme represents a key target of lithium's action in the brain (Stambolic et al., Curr. Biol. 6:1664-1668, 1996; Klein and Melton; PNAS 93:8455-8459, 1996). Inhibition of GSK3 $\beta$  may therefore be of therapeutic relevance in the treatment of BD as well as in AD patients that have affective disorders.

#### 10 *Schizophrenia*

GSK3 is involved in signal transduction cascades of multiple cellular processes, particularly during neural development. Kozlovsky et al (Am J Psychiatry 2000 May;157(5):831-3) found that GSK3 $\beta$  levels were 41% lower in the schizophrenic patients than in comparison subjects. This study indicates that schizophrenia involves neurodevelopmental pathology and that abnormal GSK3 regulation could play a role in schizophrenia. Furthermore, reduced  $\beta$ -catenin levels have been reported in patients exhibiting schizophrenia (Cotter et al., Neuroreport 9:1379-1383 (1998)).

#### *Diabetes*

20 Insulin stimulates glycogen synthesis in skeletal muscles via the dephosphorylation and thus activation of glycogen synthase. Under resting conditions, GSK3 phosphorylates and inactivates glycogen synthase via dephosphorylation. GSK3 is also over-expressed in muscles from Type II diabetic patients (Nikoulina et al., Diabetes 2000 Feb;49(2):263-71). Inhibition of GSK3 increases the activity of glycogen synthase thereby decreasing glucose levels by its conversion to glycogen. GSK3 inhibition may therefore be of therapeutic relevance in the treatment of Type I and Type II diabetes, diabetic neuropathy and diabetes related disorders.

#### *Hair Loss*

30 GSK3 phosphorylates and degrades  $\beta$ -catenin.  $\beta$ -catenin is an effector of the pathway for keratin synthesis.  $\beta$ -catenin stabilisation may lead to increase hair development. Mice expressing a stabilised  $\beta$ -catenin by mutation of sites phosphorylated by GSK3 undergo a

process resembling de novo hair morphogenesis (Gat et al., Cell 1998 Nov 25;95 (5):605-14)). The new follicles formed sebaceous glands and dermal papilla, normally established only in embryogenesis. Thus GSK3 inhibition may offer treatment for baldness.

5 *Oral contraceptives*

Vijayaraghavan et al. (Biol Reprod 2000 Jun; 62 (6):1647-54) reported that GSK3 is high in motile versus immotile sperm. Immunocytochemistry revealed that GSK3 is present in the flagellum and the anterior portion of the sperm head. These data suggest that GSK3 could be a key element underlying motility initiation in the epididymis and regulation of  
10 mature sperm function. Inhibitors of GSK3 could be useful as contraceptives for males.

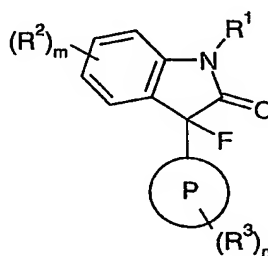
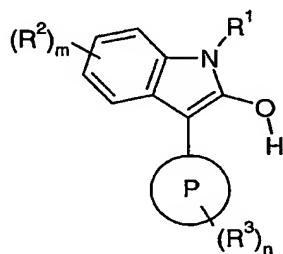
*Bone Disorders*

It has been shown that GSK3 inhibitors could be used for treatment of bone-related disorders. This has been discussed in e.g. Tobias et al., *Expert Opinion on Therapeutic*  
15 *Targets*, Feb 2002, pp 41-56.

20 DISCLOSURE OF THE INVENTION

The object of the present invention is to provide compounds having a selective inhibiting effect at GSK3 as well as having a good bioavailability. Accordingly, the present invention provides a compound of formula **Ia** or **Ib**:

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(Ia)

(Ib)

wherein:

P represents a 5- or 6-membered heteroaromatic ring containing one or two heteroatoms  
5 selected independently from N, O and S of which at least one heteroatom is nitrogen;

R<sup>1</sup> is hydrogen;

R<sup>2</sup> is selected from: C<sub>1-6</sub>alkyl, cyano, halogen, (CO)OR<sup>10</sup>, and CONR<sup>10</sup>R<sup>11</sup>;

10 R<sup>3</sup> is selected from: C<sub>1-6</sub>alkyl, cyano, nitro, (CO)OR<sup>4</sup>, C<sub>1-6</sub>alkylNR<sup>4</sup>R<sup>5</sup>, OC<sub>2-6</sub>alkylNR<sup>4</sup>R<sup>5</sup>,  
CONR<sup>4</sup>R<sup>5</sup>, SO<sub>2</sub>R<sup>4</sup>, OSO<sub>2</sub>R<sup>4</sup> and (SO<sub>2</sub>)NR<sup>4</sup>R<sup>5</sup>;

R<sup>4</sup> is selected from: hydrogen, CF<sub>3</sub> and C<sub>1-6</sub>alkyl;

15 R<sup>5</sup> is selected from: hydrogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylNR<sup>6</sup>R<sup>7</sup> and; wherein R<sup>4</sup> and R<sup>5</sup> may  
together form a 4-, 5-, 6- or 7-membered heterocyclic group containing one or more  
heteroatoms selected independently from N, O and S, wherein said heterocyclic group may  
optionally be substituted by a group Y;

20 R<sup>6</sup> and R<sup>7</sup> are independently selected from hydrogen, C<sub>1-6</sub>alkyl, (CO)C<sub>1-6</sub>alkyl, and wherein  
R<sup>6</sup> and R<sup>7</sup> may together form a 5- or 6-membered heterocyclic group containing one or  
more heteroatoms, selected independently from N, O and S, wherein said heterocyclic  
group may optionally be substituted by a group Y;

25 R<sup>8</sup> and R<sup>9</sup> are independently selected from: hydrogen and C<sub>1-6</sub>alkyl and wherein R<sup>8</sup> and R<sup>9</sup>  
may together form a 5- or 6-membered heterocyclic group containing one or more  
heteroatoms, selected independently from N, O and S;

30 R<sup>10</sup> is selected from hydrogen and C<sub>1-6</sub>alkyl;

R<sup>11</sup> is selected from hydrogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylCN, C<sub>0-6</sub>alkylaryl, C<sub>2-6</sub>alkylOR<sup>8</sup>, C<sub>1-6</sub>alkyl(CO)NR<sup>6</sup>R<sup>7</sup>, C<sub>1-6</sub>alkyl(SO<sub>2</sub>)R<sup>6</sup>, C<sub>1-6</sub>alkyl(SO<sub>2</sub>)NR<sup>6</sup>R<sup>7</sup>, C<sub>0-6</sub>alkylheteroaryl, C<sub>0-6</sub>alkylC<sub>3-6</sub>heterocyclic group and C<sub>1-6</sub>alkylNR<sup>6</sup>R<sup>7</sup>; and wherein any C<sub>0-6</sub>alkylaryl and C<sub>0-6</sub>alkylheteroaryl may be substituted by one or more group Z; and wherein any C<sub>0-6</sub>alkylC<sub>3-6</sub>heterocyclic group may be substituted by one or more group Y;

Z is selected from halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, OCF<sub>3</sub> and CF<sub>3</sub>;

Y is selected from: oxo, C<sub>2-6</sub>alkylOR<sup>8</sup>, C<sub>1-6</sub>alkyl, C<sub>0-6</sub>alkylaryl, C<sub>0-6</sub>alkylheteroaryl, OR<sup>8</sup> and C<sub>2-6</sub>alkylNR<sup>8</sup>R<sup>9</sup>;

m is 0, 1, 2, 3 or 4;

n is 0, 1, 2, 3 or 4;

as a free base or a salt, or a tautomer thereof.

One aspect of the invention relates to compounds of formula **Ia** or **Ib**, wherein:

P represents a 6-membered heteroaromatic ring containing one heteroatom selected independently from N and O;

R<sup>2</sup> is selected from: cyano, halogen, (CO)OR<sup>10</sup>, and CONR<sup>10</sup>R<sup>11</sup>;

R<sup>3</sup> is selected from: cyano, nitro, C<sub>1-6</sub>alkylNR<sup>4</sup>R<sup>5</sup>, OC<sub>2-6</sub>alkylNR<sup>4</sup>R<sup>5</sup>, CONR<sup>4</sup>R<sup>5</sup>, and (SO<sub>2</sub>)NR<sup>4</sup>R<sup>5</sup>;

R<sup>4</sup> is selected from: hydrogen and C<sub>1-6</sub>alkyl;

R<sup>5</sup> is selected from: C<sub>1-6</sub>alkyl and C<sub>1-6</sub>alkylNR<sup>6</sup>R<sup>7</sup> and; wherein R<sup>4</sup> and R<sup>5</sup> may together form a 5- or 6-membered heterocyclic group containing one or more heteroatoms selected independently from N and O, wherein said heterocyclic group may optionally be substituted by a group Y;

R<sup>6</sup> and R<sup>7</sup> are independently selected from hydrogen, (CO)C<sub>1-6</sub>alkyl, and wherein R<sup>6</sup> and R<sup>7</sup> may together form a 5- or 6-membered heterocyclic group containing one or more heteroatoms, selected independently from N and O, wherein said heterocyclic group may optionally be substituted by a group Y;

R<sup>8</sup> and R<sup>9</sup> are independently selected from: hydrogen and C<sub>1-6</sub>alkyl and wherein R<sup>8</sup> and R<sup>9</sup> may together form a 5- or 6-membered heterocyclic group containing one or more heteroatoms, selected independently from N and O;

R<sup>10</sup> is selected from hydrogen and C<sub>1-6</sub>alkyl;

R<sup>11</sup> is selected from hydrogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylCN, C<sub>0-6</sub>alkylaryl, C<sub>2-6</sub>alkylOR<sup>8</sup>, C<sub>1-6</sub>alkyl(CO)NR<sup>6</sup>R<sup>7</sup>, C<sub>1-6</sub>alkyl(SO<sub>2</sub>)R<sup>6</sup>, C<sub>1-6</sub>alkyl(SO<sub>2</sub>)NR<sup>6</sup>R<sup>7</sup>, C<sub>0-6</sub>alkylheteroaryl, C<sub>0-6</sub>alkylC<sub>3-6</sub>heterocyclic group and C<sub>1-6</sub>alkylNR<sup>6</sup>R<sup>7</sup>; and wherein any C<sub>0-6</sub>alkylaryl may be substituted by one or more group Z;

Z is selected from halo, C<sub>1-6</sub>alkoxy, OCF<sub>3</sub> and CF<sub>3</sub>;

Y is selected from: oxo, C<sub>2-6</sub>alkylOR<sup>8</sup>, C<sub>1-6</sub>alkyl and C<sub>2-6</sub>alkylNR<sup>8</sup>R<sup>9</sup>;

m is 1 or 2;

n is 1.

Another aspect of the invention relates to compounds of formula **Ia** or **Ib**, wherein P is pyridine.

Another aspect of the invention relates to compounds of formula **Ia** or **Ib**, wherein R<sup>2</sup> is selected from: cyano, (CO)OR<sup>10</sup>, and CONR<sup>10</sup>R<sup>11</sup>.

Yet another aspect of the invention relates to compounds of formula **Ia** or **Ib**, wherein  $R^2$  is  $\text{CONR}^{10}\text{R}^{11}$ ; and  $R^{11}$  is selected from hydrogen,  $\text{C}_{1-6}\text{alkyl}$ ,  $\text{C}_{1-6}\text{alkylCN}$ ,  $\text{C}_{2-6}\text{alkylOR}^8$ ,  $\text{C}_{0-6}\text{alkylaryl}$ ,  $\text{C}_{0-6}\text{alkylheteroaryl}$ ; and wherein any  $\text{C}_{0-6}\text{alkylaryl}$  and  $\text{C}_{0-6}\text{alkylheteroaryl}$  may be substituted by one or more group Z; and wherein Z is selected from  $\text{C}_{1-6}\text{alkoxy}$ ,  $\text{OCF}_3$  and  $\text{CF}_3$ .

Yet another aspect of the invention relates to compounds of formula **Ia** or **Ib**, wherein  $R^3$  is selected from:  $\text{C}_{1-6}\text{alkylNR}^4\text{R}^5$ ,  $\text{OC}_{2-6}\text{alkylNR}^4\text{R}^5$ ,  $\text{CONR}^4\text{R}^5$ , and  $(\text{SO}_2)\text{NR}^4\text{R}^5$ ; and wherein  $R^4$  and  $R^5$  may together form a 6-membered heterocyclic group containing one or two heteroatoms selected independently from N and O, wherein said heterocyclic group may optionally be substituted by a group Y, and wherein Y may be  $\text{C}_{1-6}\text{alkyl}$ .

Yet another aspect of the invention relates to compounds of formula **Ia** or **Ib**, wherein  $R^3$  is selected from:  $\text{C}_{1-6}\text{alkylNR}^4\text{R}^5$ ,  $\text{OC}_{2-6}\text{alkylNR}^4\text{R}^5$ ,  $\text{CONR}^4\text{R}^5$ , and  $(\text{SO}_2)\text{NR}^4\text{R}^5$ ; and  $R^5$  is  $\text{C}_{1-6}\text{alkylNR}^6\text{R}^7$  and wherein  $R^6$  and  $R^7$  may together form a 5- or 6-membered heterocyclic group containing one or two heteroatoms, selected independently from N and O, wherein said heterocyclic group may optionally be substituted by a group Y.

Yet another aspect of the invention relates to compounds of formula **Ia** or **Ib**, wherein  $R^3$  is  $\text{C}_{1-6}\text{alkylNR}^4\text{R}^5$ ; and wherein  $R^4$  and  $R^5$  may together form a 6-membered heterocyclic group containing one or two heteroatoms selected independently from N and O, wherein said heterocyclic group may optionally be substituted by a group Y and wherein Y may be  $\text{C}_{1-6}\text{alkyl}$  or oxo.

In a further aspect of the invention the following compounds are provided:

2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)carbonyl]pyridin-2-yl}-1*H*-indole-6-carbonitrile hydrochloride;

6-(6-Cyano-2-hydroxy-1*H*-indol-3-yl)-*N*-(2-morpholin-4-ylethyl)nicotinamide

hydrochloride;

- 6-(6-Cyano-2-hydroxy-1*H*-indol-3-yl)-*N*-methyl-*N*-(2-pyrrolidin-1-ylethyl)nicotinamide hydrochloride;
- 6-(6-Cyano-2-hydroxy-1*H*-indol-3-yl)-*N*-(2-(dimethylamino)ethyl)-*N*-methylnicotinamide hydrochloride;
- 5 6-(6-Cyano-2-hydroxy-1*H*-indol-3-yl)-*N*-(2-pyrrolidin-1-ylethyl)pyridine-3-sulfonamide hydrochloride;
- 2-Hydroxy-3-[5-(piperazine-1-sulfonyl)pyridin-2-yl]-1*H*-indole-6-carbonitrile hydrochloride;
- 3-[5-({4-[2-(Dipropylamino)ethyl]piperazin-1-yl}sulfonyl)pyridin-2-yl]-2-hydroxy-1*H*-
- 10 indole-6-carbonitrile hydrochloride;
- 2-Hydroxy-3-(5-{[4-(2-morpholin-4-ylethyl)piperazin-1-yl]sulfonyl}pyridin-2-yl)-1*H*-indole-6-carbonitrile hydrochloride;
- 2-Hydroxy-3-(5-{[4-(2-pyrrolidin-1-ylethyl)piperazin-1-yl]sulfonyl}pyridin-2-yl)-1*H*-indole-6-carbonitrile hydrochloride;
- 15 2-Hydroxy-3-(5-{[4-(2-methoxyethyl)piperazin-1-yl]sulfonyl}pyridin-2-yl)-1*H*-indole-6-carbonitrile hydrochloride;
- 2-Hydroxy-*N*-(3-methoxypropyl)-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride;
- 2-Hydroxy-*N*-(2-methoxyethyl)-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-
- 20 carboxamide hydrochloride;
- 2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-*N*-(pyridin-2-ylmethyl)-1*H*-indole-5-carboxamide hydrochloride;
- 2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-*N*-(2-thienylmethyl)-1*H*-indole-5-carboxamide hydrochloride;
- 25 2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-*N*-[2-(2-oxoimidazolidin-1-yl)ethyl]-1*H*-indole-5-carboxamide hydrochloride;
- N*-[2-(Acetylamino)ethyl]-2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxamide hydrochloride;
- 2-Hydroxy-*N*-(2-methoxybenzyl)-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-
- 30 carboxamide hydrochloride;
- 2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-*N*-[4-(trifluoromethyl)benzyl]-1*H*-indole-5-carboxamide hydrochloride;

- 2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-*N*-[2-(trifluoromethyl)benzyl]-1*H*-indole-5-carboxamide hydrochloride;
- 2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-*N*-[2-(trifluoromethoxy)benzyl]-1*H*-indole-5-carboxamide hydrochloride;
- 5 2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-*N*-[4-(trifluoromethoxy)benzyl]-1*H*-indole-5-carboxamide hydrochloride;
- 3-{5-[(Diethylamino)methyl]pyridin-2-yl}-2-hydroxy-*N*-(2-thienylmethyl)-1*H*-indole-5-carboxamide hydrochloride;
- 3-{5-[(Diethylamino)methyl]pyridin-2-yl}-2-hydroxy-*N*-(pyridin-2-ylmethyl)-1*H*-indole-5-carboxamide hydrochloride;
- 10 3-{5-[(Diethylamino)methyl]pyridin-2-yl}-2-hydroxy-*N*-(2-methoxyethyl)-1*H*-indole-5-carboxamide hydrochloride;
- 2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-*N*-(tetrahydrofuran-2-ylmethyl)-1*H*-indole-5-carboxamide hydrochloride;
- 15 *N*-Benzyl-2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxamide hydrochloride;
- 2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-*N*-propyl-1*H*-indole-5-carboxamide hydrochloride;
- 2-Hydroxy-*N*-(2-methoxyphenyl)-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride;
- 20 2-Hydroxy-*N*-(4-methoxyphenyl)-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride;
- 2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-*N*-(pyridin-3-ylmethyl)-1*H*-indole-5-carboxamide hydrochloride;
- 25 2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-*N*-(pyridin-4-ylmethyl)-1*H*-indole-5-carboxamide hydrochloride;
- 2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-*N*-(pyridin-2-ylmethyl)-1*H*-indole-5-carboxamide hydrochloride;
- N*-[2-(Aminosulfonyl)ethyl]-2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxamide hydrochloride;
- 30 2-Hydroxy-*N*-[2-(methylsulfonyl)ethyl]-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxamide hydrochloride;

- 3-(5-Cyanopyridin-2-yl)-2-hydroxy-*N*-{2-[(4-methylpiperazin-1-yl)sulfonyl]ethyl}-1*H*-indole-5-carboxamide hydrochloride;
- 2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxamide hydrochloride;
- 5 2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-sulfonamide hydrochloride;
- 2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride;
- 2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-6-carboxamide hydrochloride;
- 10 3-[5-({4-[2-(Dimethylamino)ethyl]piperazin-1-yl}sulfonyl)pyridin-2-yl]-2-hydroxy-1*H*-indole-6-carbonitrile hydrochloride;
- 2-Hydroxy-*N*-(2-methoxyethyl)-3-(5-nitropyridin-2-yl)-1*H*-indole-5-carboxamide hydrochloride;
- 15 *N*-(2-Cyanoethyl)-2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxamide hydrochloride;
- 2-Hydroxy-*N*-[2-(1*H*-imidazol-4-yl)ethyl]-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride;
- N*-Benzyl-2-hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride;
- 20 2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-*N*-propyl-1*H*-indole-5-carboxamide hydrochloride;
- 2-Hydroxy-*N*-(2-methoxyethyl)-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride;
- 25 *N*-[2-(Dimethylamino)ethyl]-2-hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride;
- 3-(5-Cyanopyridin-2-yl)-2-hydroxy-*N*-(2-methoxyethyl)-1*H*-indole-5-carboxamide hydrochloride;
- 2-Hydroxy-3-[5-(piperidin-1-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxamide hydrochloride;
- 30 2-Hydroxy-*N*-methyl-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxamide hydrochloride;

- 6-Bromo-2-hydroxy-*N*-methyl-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride;
- 6-Bromo-2-hydroxy-*N*-isopropyl-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride;
- 5 6-Bromo-2-hydroxy-*N*-(2-methoxyethyl)-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride;
- 6-Bromo-2-hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-*N*-(tetrahydrofuran-2-ylmethyl)-1*H*-indole-5-carboxamide hydrochloride;
- 6-Bromo-2-hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-*N*-(2-pyrrolidin-1-ylethyl)-1*H*-indole-5-carboxamide hydrochloride;
- 10 *N*-[3-(Dimethylamino)propyl]-2-hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride;
- 2-Hydroxy-*N*-(2-methoxyethyl)-3-[5-(morpholin-4-ylsulfonyl)pyridin-2-yl]-1*H*-indole-5-carboxamide hydrochloride;
- 15 2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-*N*-pyridin-3-yl-1*H*-indole-5-carboxamide hydrochloride;
- 2-Hydroxy-*N*-(2-methoxybenzylamide)-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride;
- 2-Hydroxy-*N*-(3-methoxybenzylamide)-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride;
- 20 2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-indole-5-carboxamide hydrochloride;
- 2-Hydroxy-*N*-(4-methoxybenzylamide)-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride;
- 25 *N*-(Cyanomethyl)-2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxamide hydrochloride;
- N*-(2-Furylmethyl)-2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxamide hydrochloride;
- 2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}-1*H*-indole-6-carbonitrile hydrochloride;
- 30 2-Hydroxy-3-[5-(piperidin-1-ylmethyl)pyridin-2-yl]-1*H*-indole-6-carbonitrile hydrochloride;



- 2-Hydroxy-3-{5-[(3-oxopiperazin-1-yl)methyl]pyridin-2-yl}-1*H*-indole-6-carbonitrile hydrochloride;
- 2-Hydroxy-3-[6-(2-morpholin-4-ylethoxy)pyrimidin-4-yl]-1*H*-indole-6-carbonitrile hydrochloride;
- 5 3-{6-[2-(Diisopropylamino)ethoxy]pyrimidin-4-yl}-2-hydroxy-1*H*-indole-6-carbonitrile hydrochloride;
- 2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxylic acid hydrochloride;
- 2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-*N*-[3-(2-oxopyrrolidin-1-yl)propyl]-1*H*-indole-5-carboxamide hydrochloride;
- 10 2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-*N*-(2-thienylmethyl)-1*H*-indole-5-carboxamide hydrochloride;
- 2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-*N*-[2-(2-oxoimidazolidin-1-yl)ethyl]-1*H*-indole-5-carboxamide hydrochloride;
- 15 2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-*N*-[2-(2-thienyl)ethyl]-1*H*-indole-5-carboxamide hydrochloride;
- N*-[2-(Acetyl amino)ethyl]-2-hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride;
- N*-(2-Cyanoethyl)-2-hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride;
- 20 *N*-[2-(Aminosulfonyl)ethyl]-2-hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride;
- N*-(Cyanomethyl)-2-hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride;
- 25 2-Hydroxy-3-[5-(4-methylpiperazine-1-sulfonyl)pyridin-2-yl]-1*H*-indole-5-carboxylic acid carbamoylmethylamide hydrochloride;
- 2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-*N*-[2-(methylsulfonyl)ethyl]-1*H*-indole-5-carboxamide hydrochloride;
- Methyl 3-fluoro-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-2-oxoindoline-5-carboxylate hydrochloride;
- 30 3-(5-Diethylaminomethyl-pyridin-2-yl)-2-hydroxy-1*H*-indole-5-carboxylic acid (2-methanesulfonyl-ethyl)-amide hydrochloride;

as a free base or another salt than hydrochloride, or a tautomer thereof;

- 2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carbonitrile;  
5 3-(4-Cyanopyridin-2-yl)-2-hydroxy-*N*-(2-methoxyethyl)-1*H*-indole-5-carboxamide;  
2-Hydroxy-3-[5-(4-methylpiperazine-1-sulfonyl)pyridin-2-yl]-1*H*-indole-5-carboxylic acid  
(2-carbamoylethyl)amide;  
2-Hydroxy-3-[5-(4-methyl-piperazin-1-ylmethyl)-pyridin-2-yl]-1*H*-indole-5-carboxylic  
acid methyl ester;  
10 2-Hydroxy-3-[5-(4-methyl-piperazin-1-ylmethyl)-pyridin-2-yl]-1*H*-indole-5-carboxylic  
acid (thiophen-2-ylmethyl)-amide dihydrochloride;  
2-Hydroxy-3-[5-(4-methyl-piperazin-1-ylmethyl)-pyridin-2-yl]-1*H*-indole-5-carboxylic  
acid benzylamide dihydrochloride;  
15 as a free base or a salt, or a tautomer thereof.

In yet another aspect of the invention the above listed compounds are in the form of a pharmaceutically acceptable salt.

- 20 In yet another aspect of the invention the following compounds, which are useful as intermediates in the preparation of compounds of formula I, are provided:

- 6-Chloronicotinic acid 1-oxide;  
Ethyl 6-chloronicotinate 1-oxide;  
25 1-[(6-Chloro-1-oxidopyridin-3-yl)carbonyl]-4-methylpiperazine;  
*tert*-Butyl 4-[(6-chloropyridin-3-yl)sulfonyl]piperazine-1-carboxylate ;  
(2-{4-[(6-Chloropyridin-3-yl)sulfonyl]piperazin-1-yl}ethyl)dipropylamine;  
4-(2-{4-[(6-Chloropyridin-3-yl)sulfonyl]piperazin-1-yl}ethyl)morpholine;  
1-[(6-Chloropyridin-3-yl)sulfonyl]-4-(2-pyrrolidin-1-ylethyl)piperazine;  
30 1-[(6-Chloropyridin-3-yl)sulfonyl]-4-(2-methoxyethyl)piperazine;  
6-Chloro-*N*-(2-pyrrolidin-1-ylethyl)pyridine-3-sulfonamide;

- (2-{4-[(6-Chloropyridin-3-yl)sulfonyl]piperazin-1-yl}ethyl)dimethylamine;  
2-Oxo-*N*-(pyridin-2-ylmethyl)indoline-5-carboxamide;  
2-Oxo-*N*-(2-thienylmethyl)indoline-5-carboxamide;  
2-Oxo-*N*-[2-(2-oxoimidazolidin-1-yl)ethyl]indoline-5-carboxamide;  
5 *N*-[2-(Acetylamino)ethyl]-2-oxoindoline-5-carboxamide;  
*N*-(3-Methoxypropyl)-2-oxoindoline-5-carboxamide;  
6-Bromo-*N*-isopropyl-2-oxoindoline-5-carboxamide;  
6-Bromo-*N*-(2-methoxyethyl)-2-oxoindoline-5-carboxamide;  
6-Bromo-2-oxo-*N*-(tetrahydrofuran-2-ylmethyl)indoline-5-carboxamide;  
10 6-Bromo-2-oxo-*N*-(2-pyrrolidin-1-ylethyl)indoline-5-carboxamide;  
*N*-[3-(Dimethylamino)propyl]-2-oxoindoline-5-carboxamide;  
*N*-(2-Methoxybenzyl)-2-oxoindoline-5-carboxamide;  
*N*-(3-Methoxybenzyl)-2-oxoindoline-5-carboxamide;  
*N*-(4-Methoxybenzyl)-2-oxoindoline-5-carboxamide;  
15 2-Oxo-*N*-(tetrahydro-2*H*-pyran-4-yl)indoline-5-carboxamide;  
*N*-Benzyl-2-oxoindoline-5-carboxamide;  
*N*-(2-Methoxyethyl)-2-oxoindoline-5-carboxamide;  
2-Oxo-*N*-propylindoline-5-carboxamide;  
*N*-[2-(Dimethylamino)ethyl]-2-oxoindoline-5-carboxamide;  
20 *N*-(2-Cyanoethyl)-2-oxoindoline-5-carboxamide;  
4-[(6-Chloro-1-oxidopyridin-3-yl)methyl]morpholine;  
4-[(6-Chloropyridin-3-yl)sulfonyl]morpholine;  
*N*-[(6-Chloro-1-oxidopyridin-3-yl)methyl]-*N*-ethylethanamine;  
1-[(6-Chloro-1-oxidopyridin-3-yl)methyl]-4-methylpiperazine;  
25 1-[(6-chloro-1-oxidopyridine-3-yl)methyl]piperidine;  
4-[(6-Chloro-1-oxidopyridin-3-yl)methyl]piperazin-2-one;  
*N*-(2-{4-Methylpiperazin-1-yl)sulfonyl}ethyl)-2-oxoindoline-5-carboxamide;  
4-{2-[(6-Chloropyrimidin-4-yl)oxy]ethyl}morpholine;  
*N*-(2-{4-Methylpiperazin-1-yl)sulfonyl}ethyl)-*N*-isopropylpropan-2-amine;  
30 Ethyl 6-(6-cyano-2-hydroxy-1*H*-indol-3-yl)nicotinate;  
Methyl 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxylate;  
Methyl 3-{5-[(diethylamino)methyl]pyridin-2-yl}-2-hydroxy-1*H*-indole-5-carboxylate;

Methyl 2-hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxylate;

2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxylic acid;

- 5 Methyl 3-(4-cyanopyridin-2-yl)-2-hydroxy-1*H*-indole-5-carboxylate;  
as a free base or a salt, or a tautomer thereof.

Listed below are definitions of various terms used in the specification and claims to describe the present invention.

10

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined', 'defined hereinbefore' or 'defined above' the said group encompasses the first occurring and broadest definition as well as each and all of the other definitions for that group.

15

For the avoidance of doubt it is to be understood that in this specification 'C<sub>0-6</sub>' means a carbon group having 0, 1, 2, 3, 4, 5 or 6 carbon atoms.

20

For the avoidance of doubt it is to be understood that in this specification 'C<sub>1-6</sub>' means a carbon group having 1, 2, 3, 4, 5 or 6 carbon atoms.

25

In this specification, unless stated otherwise, the term "alkyl" includes both straight and branched chain alkyl groups and may be, but is not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, t-pentyl, neo-pentyl, n-hexyl or i-hexyl, t-hexyl.

30

In this specification, unless stated otherwise, the term "cycloalkyl" refers to an optionally substituted, saturated cyclic hydrocarbon ring system. The term "C<sub>3-6</sub>cycloalkyl" may be, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

In this specification, unless stated otherwise, the term “alkylaryl”, includes both substituted and unsubstituted alkylaryl groups, which may be substituted on the alkyl and/or the aryl and may be, but are not limited to, C<sub>1-6</sub>alkylaryl, benzyl or ethylphenyl.

5 In this specification, unless stated otherwise, the term “heteroaryl” may be a monocyclic heteroaromatic, or a bicyclic fused-ring heteroaromatic group. Examples of said heteroaryl include, but are not limited to, pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, pyrazolyl, benzofuryl, indolyl, isoindolyl, benzimidazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, tetrazolyl and triazolyl.

10

In this specification, unless stated otherwise, the term “5- or 6-membered heteroaromatic ring containing one or two heteroatoms selected independently from N, O and S of which at least one atom is selected from nitrogen” includes, but is not limited to, isoxazolyl, isothiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl,  
15 thiazolyl, imidazolyl.

In this specification, unless stated otherwise, the terms “C<sub>3-6</sub>heterocyclic group”, “5- or 6-membered heterocyclic group containing one or more heteroatoms, selected independently from N, O and S” or “4-, 5-, 6- or 7-membered heterocyclic group containing one or more  
20 heteroatoms selected independently from N, O and S” may be, but are not limited to, azepanyl, azetidyl, imidazolidinyl, imidazolinyl, morpholinyl, piperazinyl, piperidyl, piperidonyl, pyrazolidinyl, pyrazolinyl, pyrrolidinyl, pyrrolinyl, tetrahydrofuranyl, tetrahydropyranyl, thiomorpholinyl.

25 In the case where a subscript is the integer 0 (zero) the group to which the subscript refers to, indicates that the group is absent, i.e. there is a direct bond between the groups.

In this specification, unless stated otherwise, the term halogen may be fluorine, chlorine, bromine or iodine.

30

The present invention relates to the use of a compound of formula **Ia** or **Ib** as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be

pharmaceutically acceptable salts, but other salts may be useful in the production of the compound of formula **Ia** or **Ib**.

Both organic and inorganic acids can be employed to form non-toxic pharmaceutically acceptable salts of the compounds of this invention. Pharmaceutically acceptable salts include, but are not limited to hydrochloride, and fumarate. These salts are readily prepared by methods known in the art.

Some compounds of formula **Ia** or **Ib** may have chiral centres and/or geometric isomeric centres (*E*- and *Z*- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomeric and geometric isomers.

Within the present invention it is to be understood that a compound of formula **Ia** or **Ib** or a salt thereof may exhibit the phenomenon of tautomerism as shown in Figure 1 below. It is to be understood that the invention encompasses any tautomeric form of a compound of formula **I** and is not to be limited merely to any one tautomeric form utilized within the formula drawings:

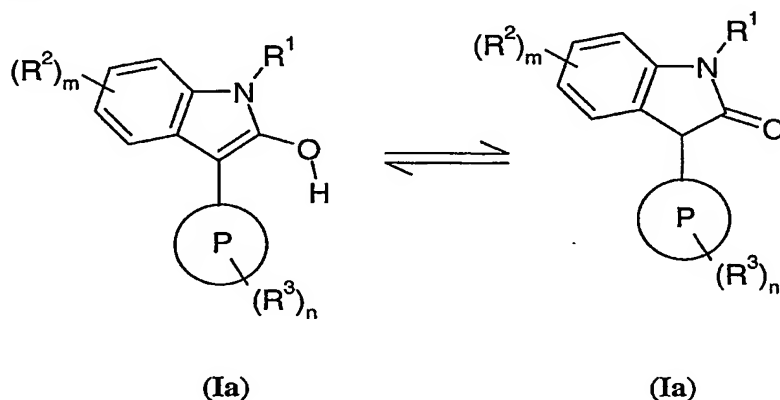


Figure 1

wherein P,  $R^1$ ,  $R^2$ ,  $R^3$ , m and n are as defined above.

An object of the invention is to provide a compound of formula **Ia** or **Ib** for therapeutic use, especially compounds that are useful for the prevention and/or treatment of conditions

associated with glycogen synthase kinase-3 (GSK3) in mammals including man. Particularly, a compound of formula **Ia** or **Ib** exhibiting a selective affinity for GSK-3.

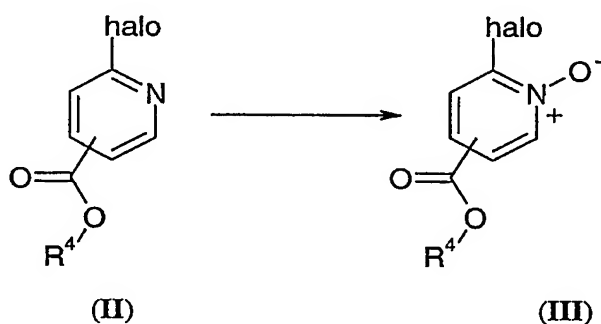
## 5 METHODS OF PREPARATION

Another aspect of the present invention provides a process for preparing a compound of formula **Ia** or **Ib** as a free base or a salt thereof. Throughout the following description of such processes it is understood that, where appropriate, suitable protecting groups will be added to, and subsequently removed from the various reactants and intermediates in a  
10 manner that will be readily understood by one skilled in the art of organic synthesis. Conventional procedures for using such protecting groups as well as examples of suitable protecting groups are for example described in "Protective Groups in Organic Synthesis", T.W. Greene, P.G.M Wutz, Wiley-Interscience, New York, 1999.

### Preparation of Intermediates

15 The process, wherein halo is halogen,  $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, R^{11}$ , n and m, unless otherwise specified, are as defined hereinbefore, comprises,

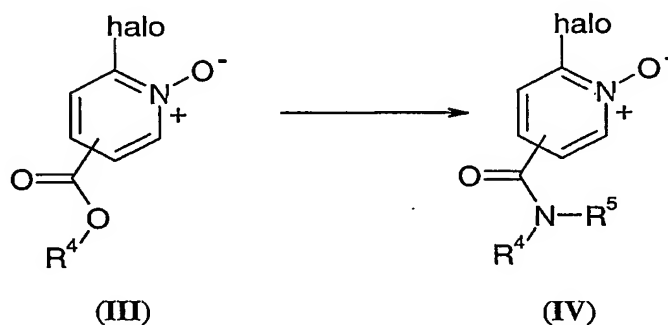
(i) oxidation of a compound of formula **II**, wherein halo is halogen e.g. fluorine, chlorine or bromine and  $R^4$  is  $C_{1-6}$ alkyl or hydrogen, to a compound of formula **III** may be carried  
20 out by



the reaction with the appropriate reagent such as urea hydroperoxide complex and trifluoroacetic acid in a suitable solvent such as acetonitrile, dichloromethane or  
25 chloroform, or 3-chloroperbenzoic acid in a suitable solvent such as toluene,

dichloromethane, chloroform or acetonitrile and the reaction may occur at a temperature between -20 °C and +80 °C.

- (ii) conversion of a compound of formula **III**, wherein halo is halogen e.g. fluorine, chlorine or bromine and R<sup>4</sup> is hydrogen, to a compound of formula **IV** may be carried out by



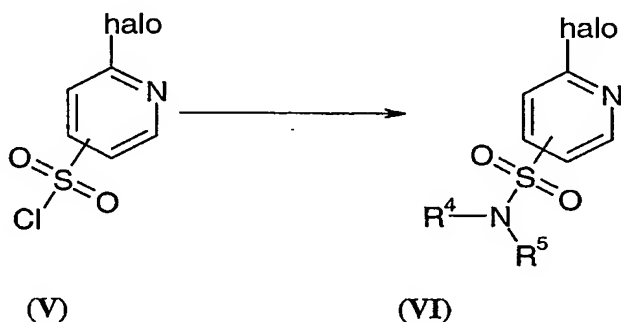
activation of the acid function in a compound of formula **III**, with

- a) a halogenation reagent such as thionyl chloride or oxalyl chlorid in a suitable solvent such as dichloromethane, chloroform or toluene or using the reagent neat and the reaction may occur at a temperature between 0 °C and +80 °C, followed by the reaction with the appropriate amine R<sup>4</sup>R<sup>5</sup>NH in a suitable solvent such as dichloromethane, chloroform, toluene or acetonitrile with or without a suitable base such as an alkali metal, an alkaline earth metal carbonate or hydroxide such as sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide or an alkylamine base such as triethylamine and the reaction may occur at a temperature between -20 °C and +80 °C, or
- b) a suitable coupling reagent such as 1,3-diisopropylcarbodiimide, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, O-(benzotriazol-1-yl)-N, N, N', N'-tetramethyluronium tetrafluoroborate, O-(benzotriazol-1-yl)-N, N, N', N'-tetramethyluronium hexafluorophosphate, 1,1'-carbonyldiimidazole or O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate where the reaction may be aided by the addition of 1-hydroxybenzotriazole hydrate and optionally a suitable base such as N,N-diisopropylethylamine and in a suitable solvent such as dichloromethane, N,N-dimethylformamide or tetrahydrofuran and the reaction may occur



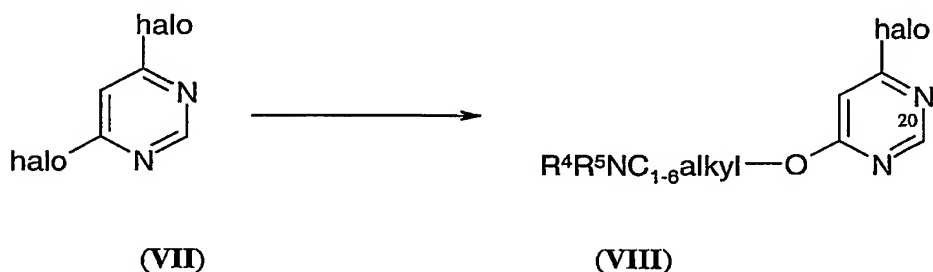
at a temperature between +20 °C and +130 °C, followed by addition of the appropriate amine  $R^4R^5NH$  and at a reaction temperature between +20 °C and +130 °C.

- (iii) conversion of a compound of formula V, wherein halo is halogen e.g. fluorine, chlorine or bromine, to a compound of formula VI may be carried out by



- the reaction with the appropriate amine  $R^4R^5NH$  in a suitable solvent such as dichloromethane, chloroform, toluene or acetonitrile with or without a suitable base such as sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide or an alkylamine base such as triethylamine and the reaction may occur at a temperature between -20 °C and +80 °C.

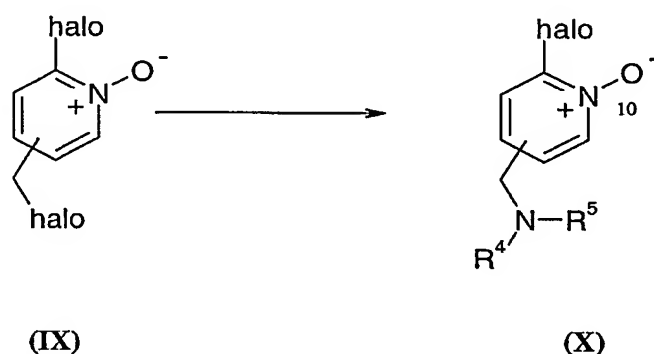
- (iv) reaction of a compound of formula VII, wherein halo is halogen e.g. fluorine chlorine, bromine, to a compound of formula VIII may be carried out by



- the reaction with an appropriate reagent  $R^4R^5NC_{2-6}alkylOH$  in a suitable solvent such as acetonitrile, dichloromethane, chloroform, toluene or *N,N*-dimethylformamide in the presence of a suitable base such as sodium carbonate, potassium carbonate, calcium

carbonate, cesium carbonate, sodium hydroxide, potassium hydroxide or sodium hydride or an alkylamine base such as triethylamine and the reaction may occur at a temperature between 0 °C and +80 °C.

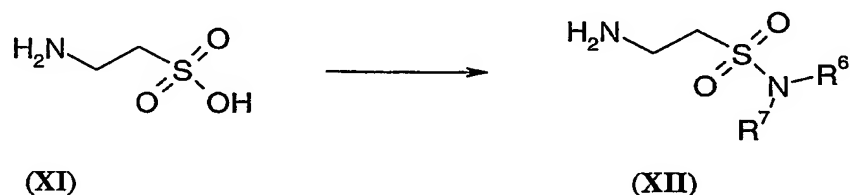
- 5 (v) Conversion of a compound of formula **IX**, wherein halo is halogen e.g. fluorine, chlorine, bromine, to a compound of formula **X** may be carried out by



15

reacting a compound of formula **IX** with an appropriate amine  $R^4R^5NH$  in a suitable solvent such as dichloromethane, chloroform, acetonitrile or *N,N*-dimethylformamide with or without a suitable base such as sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide or, an alkylamine base such as triethylamine and the reaction may occur at a temperature between 0 °C and + 120 °C.

20



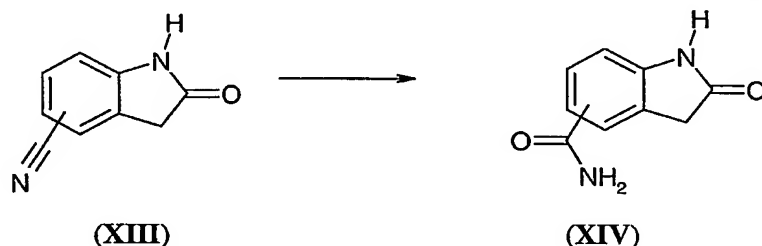
- 25 (vi) conversion of a compound of formula **XI** to a compound of formula **XII** may be carried out by the protection of the amino function in compound of formula **XI** with a suitable protecting group such as a benzyloxycarbonyl group followed by activation of the sulfonic acid function with a suitable halogenating reagent e.g. thionyl chloride or phosphorus oxychloride in a suitable solvent such as dichloromethane,

chloroform, benzene or toluene, or using the reagent neat. The reaction may occur at a temperature between 0 °C and reflux.

The formed sulfonyl chloride may be reacted with the appropriate amine  $\text{HNR}^6\text{R}^7$  in a  
5 suitable solvent such as dichloromethane, chloroform, toluene or benzene with or without a  
suitable base such as sodium carbonate, potassium carbonate, calcium carbonate, sodium  
hydroxide or an alkylamine base e.g. triethylamine and the reaction may occur at a  
temperature between -20 °C and +80 °C. The protecting group is removed in a manner  
that will be readily understood by one skilled in the art of organic synthesis.

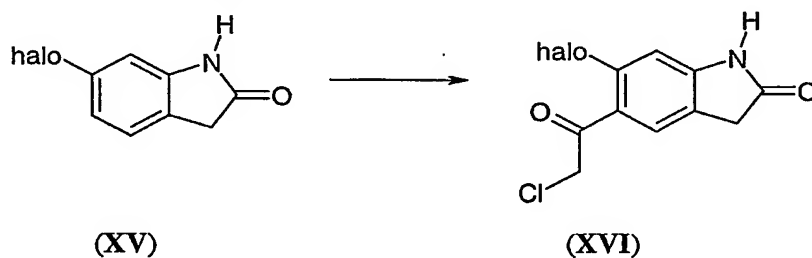
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(vii) hydrolysis of a compound of formula **XIII** to obtain a compound of formula **XIV**,



may be carried with a suitable hydrolyzing reagent such as an acid e.g. sulphuric acid at a  
15 reaction temperature between 0 °C and +100 °C.

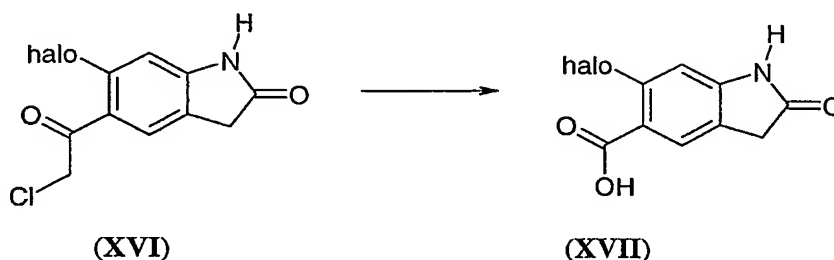
(viii) conversion of a compound of formula **XV**, wherein halo is as defined above, to  
obtain a compound of formula **XVI**,



20

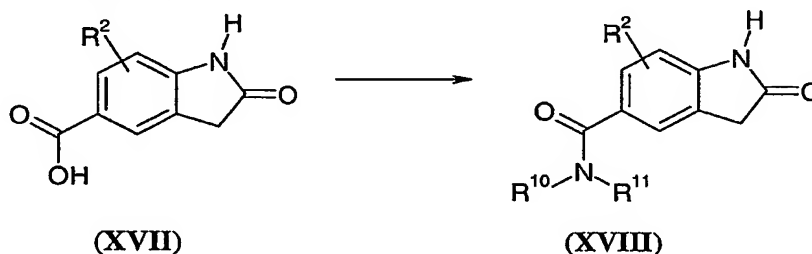
may be carried out in a suitable solvent such as carbon disulfide, dichloromethane, 1,2-  
dichlorethane in the presence of suitable reagents such as aluminum trichloride and  
chloroacetyl chloride and at a reaction temperature between 0 °C and reflux.

(ix) conversion of a compound of formula **XVI**, wherein halo is as defined above, to obtain a compound of formula **XVII**,



may be carried out in a suitable solvent such as pyridine in the presence of a suitable base such as sodium hydroxide or potassium hydroxide and at a reaction temperature between 25 °C and 90 °C.

(x) amidation of a compound of formula **XVII**, wherein  $R^2$  is halo or hydrogen, to obtain a compound of formula **XVIII**,

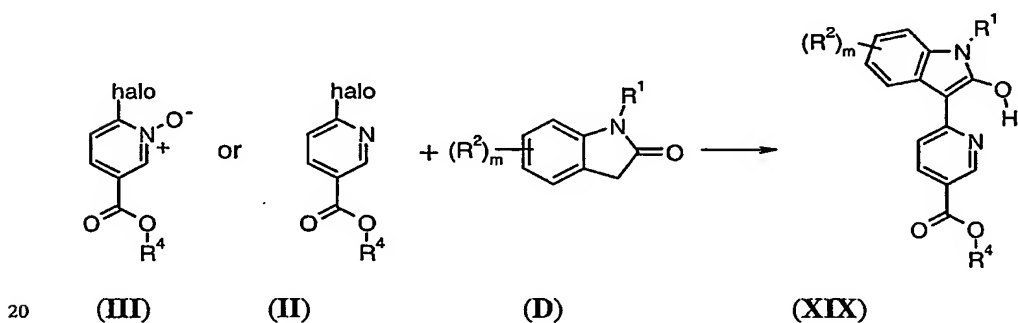


may be carried by activation of the acid function in a compound of formula **XVII**, with

a) a halogenation reagent such as thionyl chloride or oxalyl chlorid in a suitable solvent such as dichloromethane, chloroform or toluene or using the reagent neat and the reaction may occur at a temperature between 0 °C and +80 °C, followed by the reaction with the appropriate amine  $R^{10}R^{11}NH$ , e.g. compound of formula **XII**, in a suitable solvent such as dichloromethane, chloroform, toluene or acetonitrile with or without a suitable base such as an alkali metal, an alkaline earth metal carbonate or hydroxide such as sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide or an alkylamine base such as triethylamine and the reaction may occur at a temperature between -20 °C and +80 °C, or

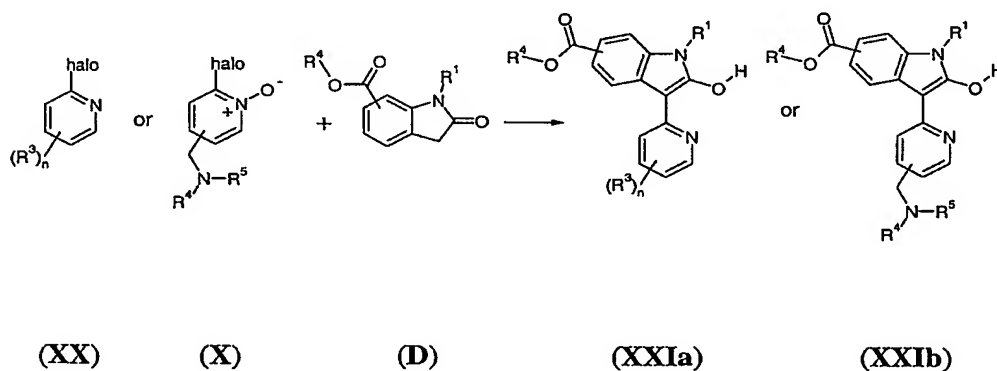
b) a suitable coupling reagent such as 1,3-diisopropylcarbodiimide, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, O-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate, O-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, 1,1'-carbonyldiimidazole or O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate where the reaction may be aided by the addition of 1-hydroxybenzotriazole hydrate and optionally a suitable base such as *N,N*-diisopropylethylamine and in a suitable solvent such as acetonitril, dichloromethane, *N,N*-dimethylformamide or tetrahydrofuran or mixtures thereof and the reaction may occur at a temperature between +20 °C and +130 °C, followed by addition of the appropriate amine  $R^{10}R^{11}NH$ , e.g. compound of formula XII, and at a reaction temperature between +20 °C and +130 °C.

(xi) reacting a compound of formula II or III, wherein  $R^4$  is  $C_{1-6}$ alkyl and halo is a halogen, e.g. fluorine, chlorine or bromine, with a compound of formula D (e.g. compounds of formula XIV and XVIII) to form a compound of formula XIX,



may be carried out in an appropriate solvent such as an ether e.g. tetrahydrofuran or 1,4-dioxan, an aromatic hydrocarbon solvent such as toluene or a dipolar aprotic solvent such as *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidin-2-one or dimethylsulphoxide and the reaction may occur at a temperature between +10 °C and +150 °C.

The reaction is advantageously effected in the presence of a base. A suitable base may be an organic amine base such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, *N*-methylmorpholine, diazabicyclo[5.4.0]undec-7-ene, tetramethylguanidine or an alkali metal or an alkaline earth metal carbonate or hydroxide  
 5 such as sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide. Alternatively, such a base may be an alkali metal hydride such as sodium hydride, or an alkali metal or alkaline earth metal amide such as sodium amide, sodium bis(trimethylsilyl)amide, potassium amide or potassium bis(trimethylsilyl)amide. The *N*-oxide may be reduced by using a suitable reagent such as phosphorus trichloride in  
 10 a suitable solvent such as dichloromethane, chloroform, toluene or ethyl acetate or mixtures thereof and the reaction may occur at a temperature between 0 °C and +100 °C.



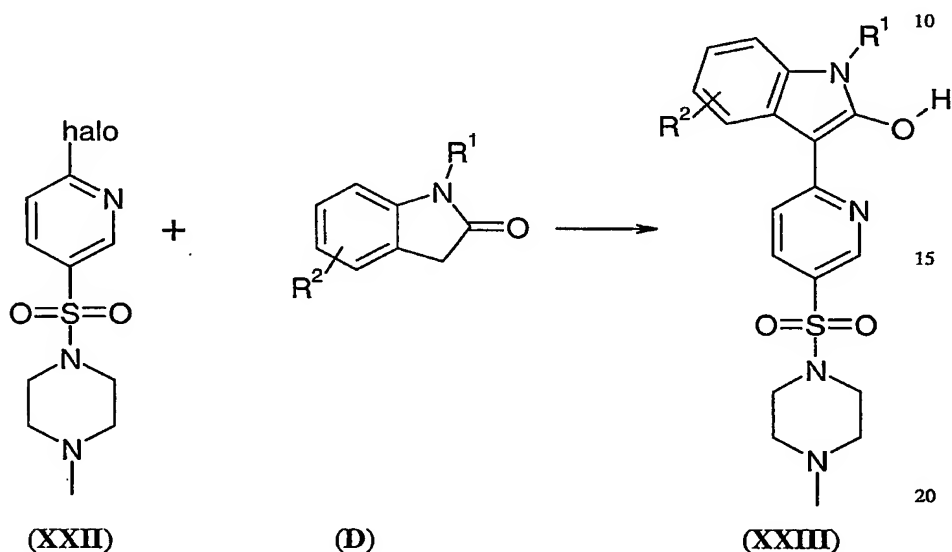
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(xii) reacting a compound of formula **XX** or **X**, wherein halo is a halogen, e.g. fluorine, chlorine or bromine, with a compound of formula **D**, wherein  $R^4$  is  $C_{1-6}$ alkyl, to form a  
 20 compound of formula **XXIa** or **XXIb** may be carried out in an appropriate solvent such as an ether e.g. tetrahydrofuran or 1,4-dioxan, an aromatic hydrocarbon solvent such as toluene or a dipolar aprotic solvent such as *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidin-2-one or dimethylsulphoxide and the reaction may occur at a temperature between +10 °C and +150 °C.

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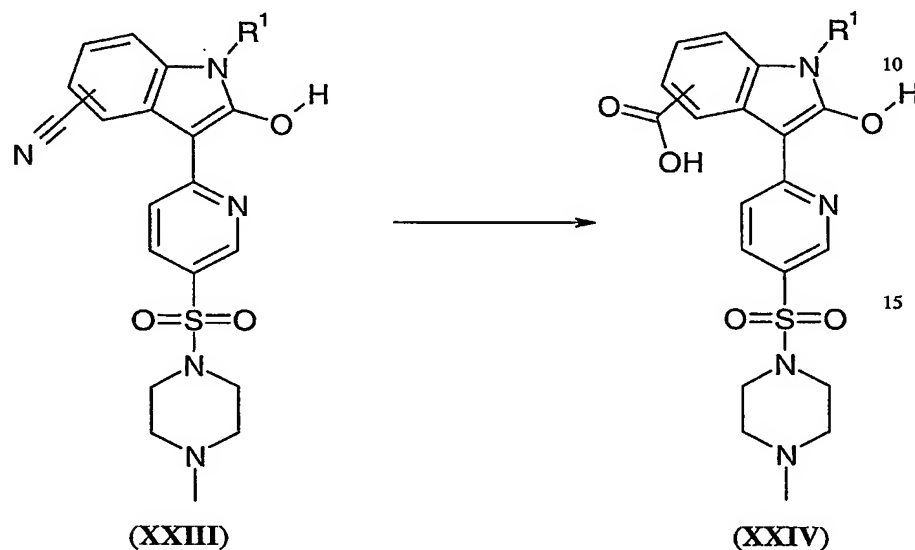
The reaction is advantageously effected in the presence of a base. A suitable base may be an organic amine base such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine,

triethylamine, morpholine, *N*-methylmorpholine, diazabicyclo[5.4.0]undec-7-ene, tetramethylguanidine or an alkali metal or an alkaline earth metal carbonate or hydroxide such as sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide. Alternatively, such a base may be an alkali metal hydride such as sodium hydride, or an alkali metal or alkaline earth metal amide such as sodium amide, sodium bis(trimethylsilyl)amide, potassium amide or potassium bis(trimethylsilyl)amide. The *N*-oxide may be reduced by using a suitable reagent such as phosphorus trichloride in a suitable solvent such as dichloromethane, chloroform, toluene or ethyl acetate or mixtures thereof and the reaction may occur at a temperature between 0 °C and +100 °C.



(xiii) reacting a compound of formula **XXII**, wherein halo is a halogen, e.g. fluorine, chlorine or bromine, with a compound of formula **D**, wherein  $R^1$  is hydrogen,  $R^2$  is cyano or  $(CO)OR^4$  and  $R^4$  is  $C_{1-6}$ alkyl, to form a compound of formula **XXIII**, may be carried out in an appropriate solvent such as an ether e.g. tetrahydrofuran or 1,4-dioxan, an aromatic hydrocarbon solvent such as toluene or a dipolar aprotic solvent such as *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidin-2-one or dimethylsulphoxide and the reaction may occur at a temperature between +10 °C and +150 °C.

The reaction is advantageously effected in the presence of a base. A suitable base may be an organic amine base such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, *N*-methylmorpholine, diazabicyclo[5.4.0]undec-7-ene, tetramethylguanidine or an alkali metal or an alkaline earth metal carbonate or hydroxide such as sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide. Alternatively, such a base may be an alkali metal hydride such as sodium hydride, or an alkali metal or alkaline earth metal amide such as sodium amide, sodium bis(trimethylsilyl)amide, potassium amide or potassium bis(trimethylsilyl)amide.



20

(xiv) converting a compound of formula **XXIII**, wherein R<sup>1</sup> is hydrogen, to a compound of formula **XXIV**, may be carried out in an appropriate solvent such as water and a suitable base such as sodium hydroxide or potassium hydroxide and the reaction may occur at a temperature between +10 °C and +150 °C, e.g. under micro wave irradiation.

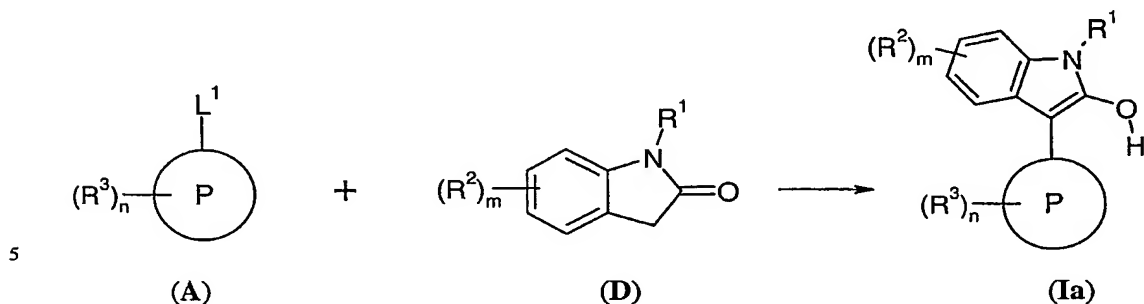
### Methods of Preparation of End products

Another object of the invention are processes **a, b, c, d, e and f** for the preparation of a compound of general formula **Ia** or **Ib**, wherein halo is halogen, **P, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>10</sup>, R<sup>11</sup>** **m** and **n**, unless otherwise specified, are defined as hereinbefore, and salts thereof.

These processes comprise:



a) reacting a compound of formula A (e.g. compound of formula VI, VIII), wherein  $L^1$  is a leaving group such as halogen, e.g. fluorine, chlorine or bromine, with a compound of formula D (e.g. compounds of formula XIV, XVIII) to form a compound of formula Ia;



The reaction of process a may be carried out in an appropriate solvent such as an ether e.g. tetrahydrofuran or 1,4-dioxan, an aromatic hydrocarbon solvent such as toluene or a dipolar aprotic solvent such as *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidin-2-one or dimethylsulphoxide and the reaction may occur at a temperature between +10 °C and +150 °C.

10

The reaction is advantageously effected in the presence of a base. A suitable base may be an organic amine base such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, *N*-methylmorpholine, diazabicyclo[5.4.0]undec-7-ene, tetramethylguanidine or an alkali metal or an alkaline earth metal carbonate or hydroxide such as sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide. Alternatively, such a base may be an alkali metal hydride such as sodium hydride, or an alkali metal or alkaline earth metal amide such as sodium amide, sodium bis(trimethylsilyl)amide, potassium amide or potassium bis(trimethylsilyl)amide.

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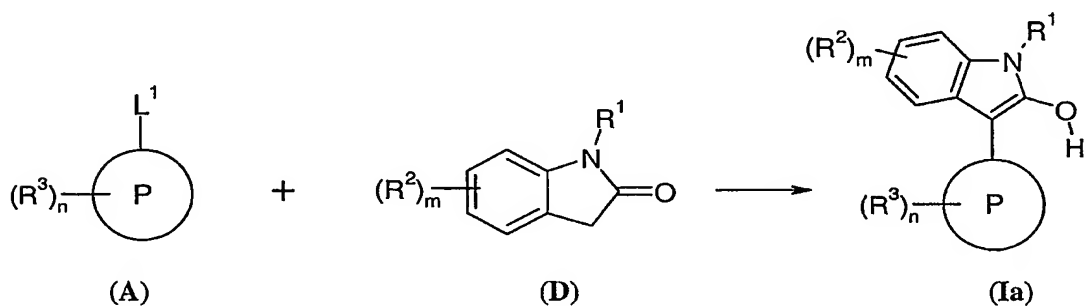
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When it is desired to obtain the acid salt, the free base may be treated with an acid such as a hydrogen halide such as hydrogen chloride or, a carboxylic acid such as fumaric acid in a suitable solvent such as tetrahydrofuran, diethyl ether, methanol, ethanol, chloroform or dichloromethane or mixtures thereof, the reaction may occur between -30 °C to +50 °C.

25

Consequently, there is provided a process for the preparation of a compound of formula **Ia** as defined above, wherein **P**,  $R^1$ ,  $R^2$  and  $R^3$ , *m* and *n*, unless otherwise specified, are defined above, comprising reacting a compound of formula **A**, wherein  $L^1$  is a leaving group, with a compound of formula **D** to form a compound of formula **Ia**;

5

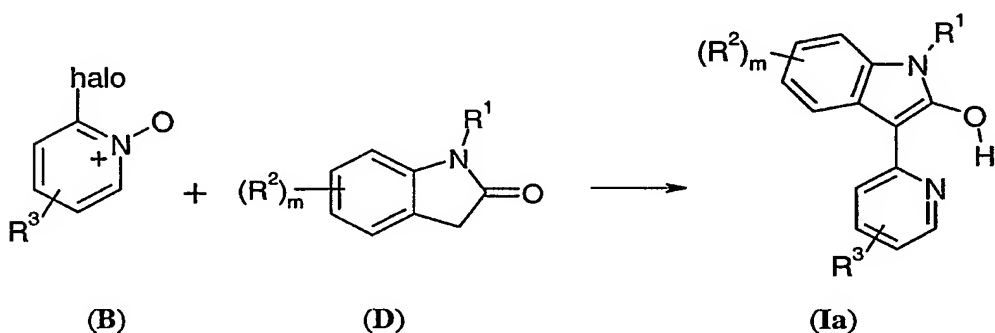


said reaction being carried out in an appropriate solvent at a temperature between +10 °C and +150 °C.

10

**b)** reacting a compound of formula **B** (e.g. compounds of formula **IV**, **X**), wherein halo is halogen, e.g. fluorine, chlorine or bromine with a compound of formula **D** (e.g. compounds of formula **XIV**, **XVIII**) to form a compound of formula **Ia**;

15



The reaction of process **b** may be carried out in an appropriate solvent such as an ether e.g. tetrahydrofuran or 1,4-dioxan, an aromatic hydrocarbon solvent such as toluene, or a dipolar aprotic solvent such as *N,N*-dimethylformamide, *N,N*-dimethylacetamide,

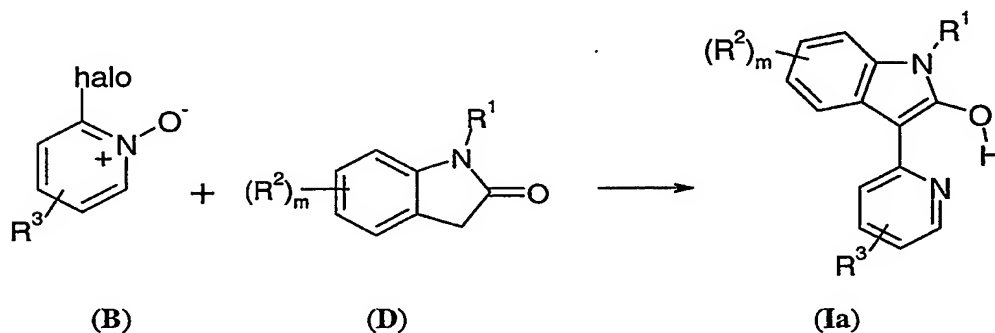
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*N*-methylpyrrolidin-2-one or dimethylsulphoxide, the reaction may occur at a temperature between +10 °C and +150 °C.

The reaction is advantageously effected in the presence of a base. Such a base may be an organic amine base such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, *N*-methylmorpholine, diazabicyclo[5.4.0]undec-7-ene, tetramethylguanidine or an alkali metal or an alkaline earth metal carbonate or hydroxide such as sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide. Alternatively, such a base may be an alkali metal hydride such as sodium hydride, an alkali metal or an alkaline earth metal amide such as sodium amide, sodium bis(trimethylsilyl)amide, potassium amide or potassium bis(trimethylsilyl)amide. The *N*-oxide may be reduced by using a suitable reagent such as phosphorus trichloride in a suitable solvent such as dichloromethane, chloroform, toluene or ethyl acetate or mixtures thereof and the reaction may occur at a temperature between 0 °C and +100 °C.

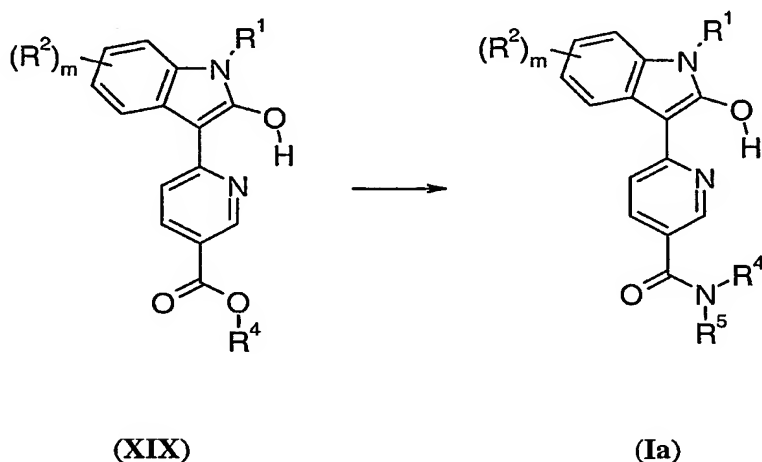
When it is desired to obtain the acid salt, the free base may be treated with an acid such as a hydrogen halide such as hydrogen chloride, or a carboxylic acid such as fumaric acid in a suitable solvent such as tetrahydrofuran, diethyl ether, methanol, ethanol, chloroform or dichloromethane or mixtures thereof, the reaction may occur between -30 °C to +50 °C.

Consequently, there is provided a process for the preparation of a compound of formula **Ia** as defined above, wherein  $R^1$ ,  $R^2$  and  $R^3$  and  $m$ , is as defined above, and halo is halogen, unless otherwise specified, comprising reacting a compound of formula **B** with a compound of formula **D** to form a compound of formula **Ia**;



said reaction being carried out in an appropriate solvent at a temperature between +10 °C and +150 °C.

- 5 c) reacting a compound of formula XIX, wherein  $R^4$  is  $C_{1-6}$ alkyl, with the appropriate amine  $HNR^4R^5$ , to form a compound of formula Ia;



10

The reaction of process c may be carried out by:

- i) the reaction of the compound of formula XIX with the appropriate amine  $R^4R^5NH$  in a suitable solvent such as benzene, dichloromethane, chloroform, toluene or acetonitrile in the presence of a suitable reagent such as trimethylaluminum and at a reaction temperature between 0 °C and reflux or,

- ii) the reaction of the compound of formula XIX with the appropriate amine  $R^4R^5NH$  neat or in a suitable solvent such as dichloromethane, chloroform, toluene or acetonitrile with or without a suitable base such as an alkali metal, an alkaline earth metal carbonate or hydroxide such as sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide or an alkyl aminebase such as triethylamine, and the reaction may occur at a temperature between -20 °C and +150 °C.

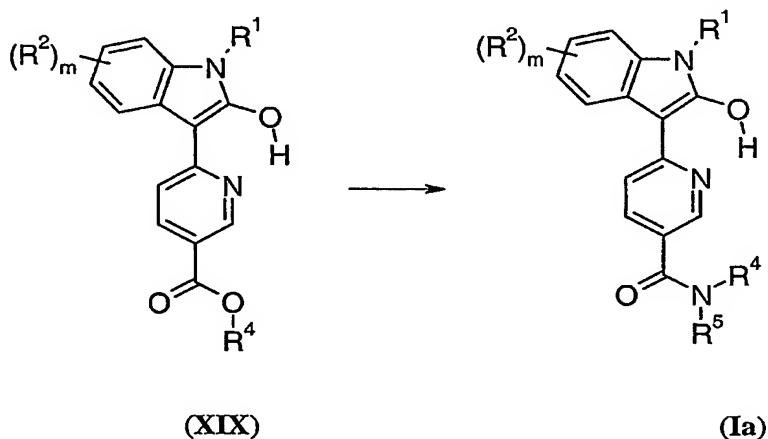
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When it is desired to obtain the acid salt, the free base may be treated with an acid such as a hydrogen halide such as hydrogen chloride, or a carboxylic acid such as fumaric acid in a suitable solvent such as tetrahydrofuran, diethyl ether, methanol, ethanol, chloroform or dichloromethane or mixtures thereof, the reaction may occur between -30 °C to +50 °C.

5

Consequently, there is provided a process for the preparation of a compound of formula **Ia** as defined above, wherein  $R^3$  is  $\text{CONR}^4\text{R}^5$ , comprising reacting a compound of formula **XIX**, wherein  $R^4$  is  $\text{C}_{1-6}$ alkyl, with the appropriate amine  $\text{HNR}^4\text{R}^5$ , to form a compound of formula **Ia**;

10



15

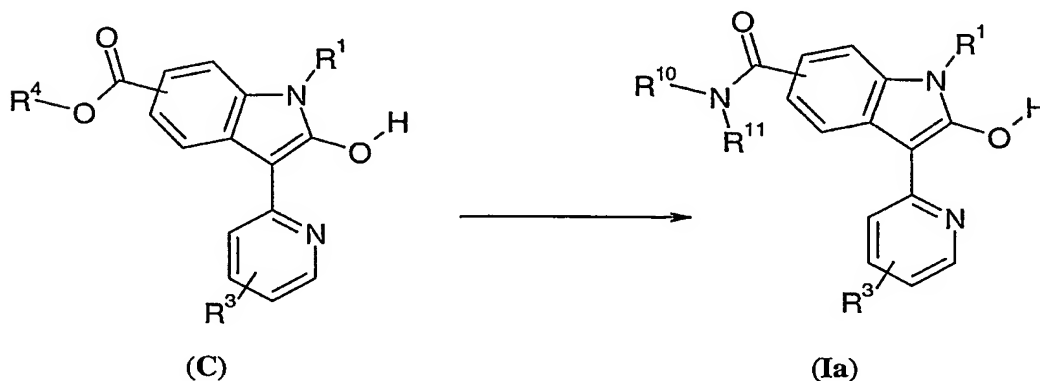
said reaction being carried out by;

i) reacting the compound of formula **XIX** with the appropriate amine  $\text{R}^4\text{R}^5\text{NH}$  in a suitable solvent in the presence of a suitable reagent at a reaction temperature between 0 °C and reflux or;

20 ii) reacting the compound of formula **XIX** with the appropriate amine  $\text{R}^4\text{R}^5\text{NH}$  neat or in a suitable solvent with or without a suitable base or an alkylamine base at a temperature between -20 °C and +150 °C.

d) amidation of a compound of formula **C** (e.g compounds of formula **XXIa**, **XXIb** and **XXIII**), wherein  $R^4$  is  $C_{1-6}$ alkyl, to form a compound of the formula **Ia** with the appropriate amine  $HNR^{10}R^{11}$ , may be carried out by

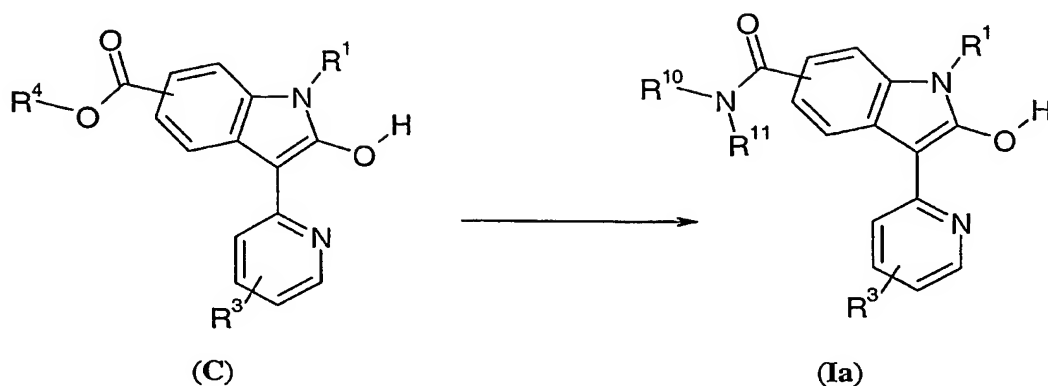
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reaction with the appropriate amine  $HNR^{10}R^{11}$  in a suitable solvent such as benzene,  
 10 toluene, hexane, heptane, dichloromethane or chloroform in the presence of trimethyl  
 aluminum and at a reaction temperature between  $-10\text{ }^{\circ}\text{C}$  and reflux.

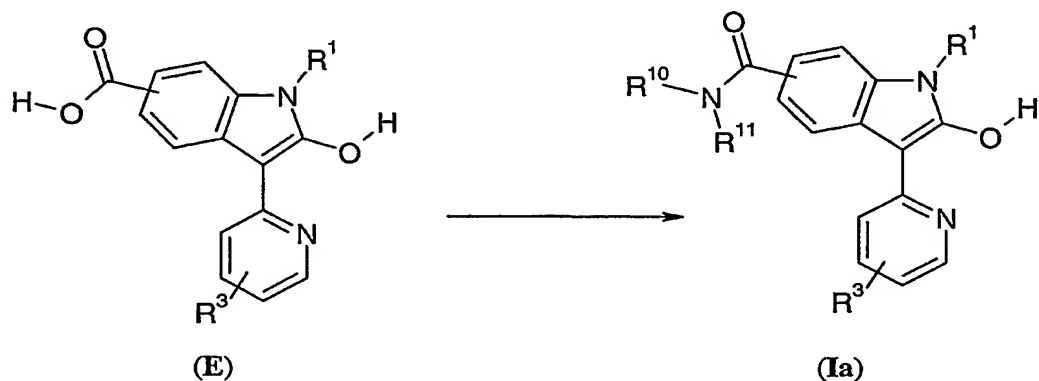
When it is desired to obtain the acid salt, the free base may be treated with an acid such as  
 a hydrogen halide such as hydrogen chloride, or a carboxylic acid such as fumaric acid in a  
 15 suitable solvent such as tetrahydrofuran, diethyl ether, methanol, ethanol, chloroform or  
 dichloromethane or mixtures thereof, the reaction may occur between  $-30\text{ }^{\circ}\text{C}$  to  $+50\text{ }^{\circ}\text{C}$ .

Consequently, there is provided a process for the preparation of a compound of formula **Ia**  
 as defined above, wherein  $R^2$  is  $CONR^{10}R^{11}$ , comprising amidation of a compound of  
 20 formula **C**, wherein  $R^4$  is  $C_{1-6}$ alkyl, to form a compound of the formula **Ia**;



said reaction being carried out with the appropriate amine  $\text{HNR}^{10}\text{R}^{11}$  in a suitable solvent  
 5 in the presence of trimethyl aluminum and at a reaction temperature between  $-10\text{ }^{\circ}\text{C}$  and  
 reflux.

e) amidation of a compound of formula **E** ( e.g. compound of formula **XXIV**), to form a  
 10 compound of the formula **Ia**, with the appropriate amine  $\text{HNR}^{10}\text{R}^{11}$ , may be carried out by



15 activation of the acid function in a compound of formula **E** (e.g compound of formula  
**XXIV**), with  
 a) a halogenation reagent such as thionyl chloride or oxalyl chlorid in a suitable solvent  
 such as methylene chloride, chloroform or toluene or using the reagent neat and the  
 reaction may occur at a temperature between  $0\text{ }^{\circ}\text{C}$  and  $+80\text{ }^{\circ}\text{C}$ , followed by the reaction

with the appropriate amine  $\text{HNR}^{10}\text{R}^{11}$  in a suitable solvent such as methylene chloride, chloroform, toluene or acetonitrile with or without a suitable base such as an alkali metal, an alkaline earth metal carbonate or hydroxide such as sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide or an alkylamine  
5 base such as triethylamine and the reaction may occur at a temperature between  $-20\text{ }^{\circ}\text{C}$  and  $+80\text{ }^{\circ}\text{C}$ , or

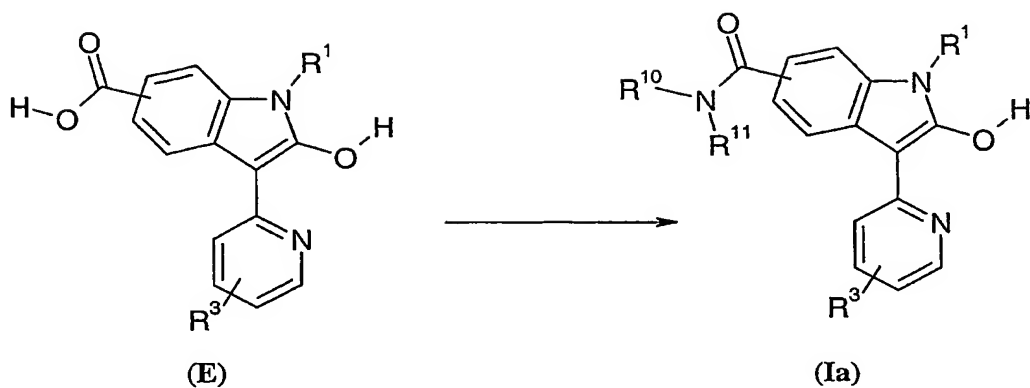
**b)** a suitable coupling reagent such as 1,3-diisopropylcarbodiimide, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide, 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, O-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate, O-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, 1,1'-carbonyldiimidazole or O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate where the  
10 reaction may be aided by the addition of 1-hydroxybenzotriazole hydrate and optionally a suitable base such as *N,N*-diisopropylethylamine and in a suitable solvent such as  
15 methylene chloride, *N,N*-dimethylformamide or tetrahydrofuran and the reaction may occur at a temperature between  $+20\text{ }^{\circ}\text{C}$  and  $+130\text{ }^{\circ}\text{C}$ , followed by addition of the appropriate amine  $\text{HNR}^{10}\text{R}^{11}$  and at a reaction temperature between  $+20\text{ }^{\circ}\text{C}$  and  $+130\text{ }^{\circ}\text{C}$ .

When it is desired to obtain the acid salt, the free base may be treated with an acid such as  
20 a hydrogen halide such as hydrogen chloride, or a carboxylic acid such as fumaric acid in a suitable solvent such as tetrahydrofuran, diethyl ether, methanol, ethanol, chloroform or dichloromethane or mixtures thereof, the reaction may occur between  $-30\text{ }^{\circ}\text{C}$  to  $+50\text{ }^{\circ}\text{C}$ .

Consequently, there is provided a process for the preparation of a compound of formula **Ia**  
25 as defined above, wherein  $\text{R}^2$  is  $\text{CONR}^{10}\text{R}^{11}$ , comprising amidation of a compound of formula **E**, to form a compound of the formula **Ia**, with the appropriate amine  $\text{HNR}^{10}\text{R}^{11}$ ;



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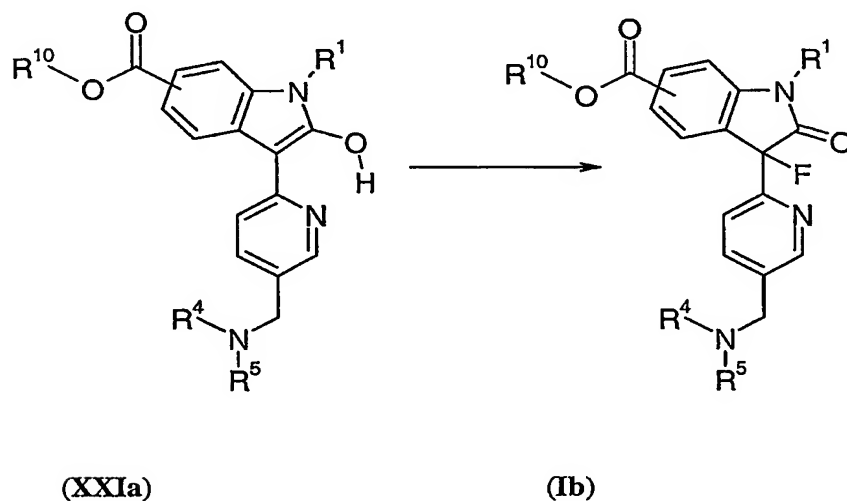


carried out by activation of the acid function in a compound of formula E with;

- 5 a) a halogenation reagent in a suitable solvent at a temperature between 0 °C and +80 °C, followed by the reaction with the appropriate amine  $\text{HNR}^{10}\text{R}^{11}$  in a suitable solvent with or without a suitable base at a temperature between -20 °C and +80 °C, or;
- b) a coupling reagent where the reaction is carried out in a suitable solvent at a temperature between +20 °C and +130 °C, followed by addition of the appropriate amine  $\text{HNR}^{10}\text{R}^{11}$ .

10

f) fluorinating a compound of formula **XXIa** to form a compound of formula **Ib**.

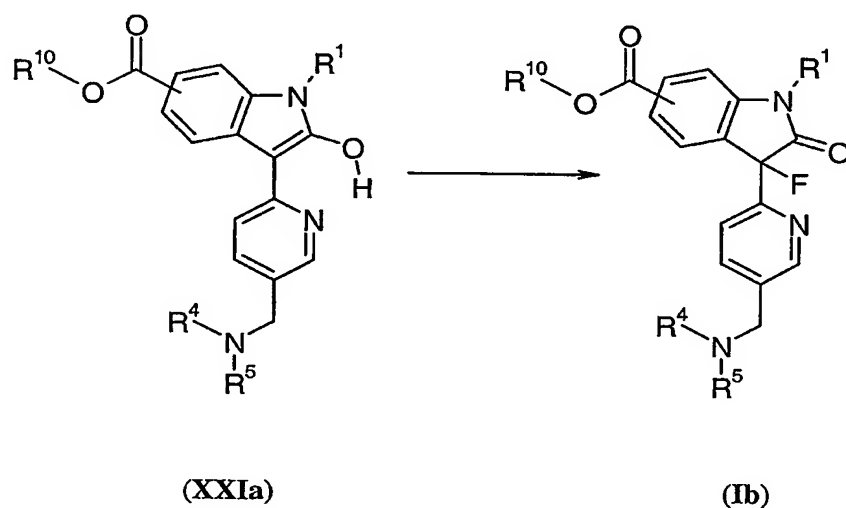


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The reaction of process f may be carried out in an appropriate solvent such as an ether e.g. tetrahydrofuran or 1,4-dioxan or mixtures thereof in the presence of a suitable fluorinating reagent such as 1-fluoro-2,4,6-trimethylpyridinium triflate and a suitable base such as n-butyllithium or sodium bis(trimethylsilyl)amide and at a reaction temperature between -40 °C and +80 °C.

When it is desired to obtain the acid salt, the free base may be treated with an acid such as a hydrogen halide such as hydrogen chloride, sulphuric acid, a sulphonic acid such as methane sulphonic acid or a carboxylic acid such as acetic or citric acid in a suitable solvent such as tetrahydrofuran, diethyl ether, methanol, ethanol, chloroform or methylene chloride or mixtures thereof, the reaction may occur between -30 °C to +50 °C.

Consequently, there is provided a process for the preparation of a compound of formula Ia as defined above, wherein  $R^3$  is  $C_{1-6}alkylNR^4R^5$ , comprising fluorinating a compound of formula XXIIa to form a compound of formula Ib.



said reaction being carried out in an appropriate solvent in the presence of a suitable fluorinating reagent and a suitable base at a reaction temperature between -40 °C and +80 °C.

Throughout the following description of such processes it is understood that, where appropriate, suitable protecting groups will be added to, and subsequently removed from, the various reactants and intermediates in a manner that will be readily understood by one skilled in the art of organic synthesis. Conventional procedures for using such protecting groups as well as examples of suitable protecting groups are described, for example, in "Protective Groups in Organic Synthesis" T.W. Green, P.G.M. Wuts, Wiley-Interscience, New York, 1999.

## WORKING EXAMPLES

### Example 1

#### **6-Chloronicotinic acid 1-oxide**

*m*-Chloroperbenzoic acid (7.46 g, 26.0 mmol) was added to a suspension of 6-chloronicotinic acid (3.14 g, 20.0 mmol) in chloroform (30 mL) at room temperature. The mixture was stirred for 24 h at 45 °C followed by cooling to 0 °C. The resulting white precipitate was filtered off, washed with chloroform (10 mL), and air-dried to give 3.22 g, (93% yield) of the title compound: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 8.72 (s, 1 H), 7.97 (d, *J* = 8.0 Hz, 1 H), 7.78 (d, *J* = 8.0 Hz, 1 H); MS (EI) *m/z* 174 and 176 (M<sup>+</sup>+1).

### Example 2

#### **Ethyl 6-chloronicotinate 1-oxide**

Urea hydroperoxid complex (1.19 g, 12.6 mmol) was added to a stirred solution of ethyl 6-chloronicotinate (1.10 g, 6.0 mmol) in acetonitrile (15 mL) at room temperature. This mixture was stirred for 10 min at 0 °C followed by slow addition of an acetonitrile solution (5 mL) of trifluoroacetic anhydride (2.52 g, 12.0 mmol). After the addition the mixture was stirred for 2 h at room temperature. Thereafter, the reaction mixture was diluted with a saturated aqueous NaHCO<sub>3</sub> solution and extracted with dichloromethane. The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to afford 0.98 g (81% yield) of the title compound as a white solid: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 8.94 (s, 1 H), 7.81 (dd, *J* =

8.4, 1.6 Hz, 1 H), 7.60 (d,  $J = 8.4$  Hz, 1 H), 4.43 (q,  $J = 7.2$  Hz, 2 H), 1.40 (t,  $J = 7.2$  Hz, 3 H); MS (EI)  $m/z$  202 and 204 ( $M^+ + 1$ ).

### Example 3

#### 5 1-[(6-Chloro-1-oxidopyridin-3-yl)carbonyl]-4-methylpiperazine

6-Chloronicotinic acid 1-oxide (0.347 g, 2.0 mmol) and 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (0.544 g, 2.2 mmol) were mixed in chloroform (8 mL) at 0 °C. 1-Methylpiperazine (0.30 g, 3.0 mmol) was added after 5 min and the reaction mixture was stirred for 16 h at room temperature. The solvent was removed *in vacuo* and the residual  
10 oil was purified on a silica gel column using chloroform/methanol/triethylamine, (100:20:1), as the eluent to give 0.18 g, (35% yield) of the title compound as a brownish solid:  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  8.56 (s, 1 H), 7.90 (d,  $J = 8.0$  Hz, 1 H), 7.39 (d,  $J = 8.0$  Hz, 1 H), 3.63 (br s, 2 H), 3.39 (br s, 2 H), 2.43 (br s, 2 H), 2.34 (br s, 2 H), 2.25 (s, 3 H); MS (EI)  $m/z$  256 and 258 ( $M^+ + 1$ ).

15

### Example 4

#### *tert*-Butyl 4-[(6-chloropyridin-3-yl)sulfonyl]piperazine-1-carboxylate

6-Chloropyridine-3-sulfonyl chloride (0.318 g, 1.5 mmol; described in: Naegeli, C. et al. *Helv. Chim. Acta.* **1938**, *21*, 1746-1750) was added to a suspension of potassium carbonate  
20 (0.276 g, 2.0 mmol) in dichloromethane (3 mL) at room temperature. The mixture was stirred for 5 min at 0 °C followed by the addition of *tert*-butyl 1-piperazinecarboxylate (0.363 g, 2.0 mmol). The resulting reaction mixture was allowed to stir for 16 h at room temperature and the reaction mixture was filtered and the organic solution was concentrated *in vacuo*. The residue was purified on a silica gel column using heptane/ethyl  
25 acetate, (2:1), as the eluent to afford 0.188 g (35% yield) of the title compound as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  8.74 (d,  $J = 2.0$  Hz, 1 H), 7.96 (dd,  $J = 8.4, 2.8$  Hz, 1 H), 7.51 (d,  $J = 8.4$  Hz, 1 H), 3.53 (t,  $J = 5.2$  Hz, 4 H), 3.03 (t,  $J = 5.2$  Hz, 4 H), 1.42 (s, 9 H); MS (EI)  $m/z$  362 ( $M^+ + 1$ ).

30 The following Examples, 5-9, were prepared as described for Example 4.

### Example 5

**(2-{4-[(6-Chloropyridin-3-yl)sulfonyl]piperazin-1-yl}ethyl)dipropylamine**

Starting material: 1-(2-dipropylaminoethyl)piperazine (0.32 g, 1.5 mmol). Purification on a silica gel column using chloroform/methanol/triethylamine, (100:20:1), as the eluent gave 0.24 g (41% yield) of the title compound as a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  8.574 (d,  $J = 2.4$  Hz, 1 H), 7.97 (dd,  $J = 8.0, 2.4$  Hz, 1 H), 7.50 (d,  $J = 8.0$  Hz, 1 H), 3.07 (br s, 4 H), 2.58 (t,  $J = 4.8$  Hz, 4 H), 2.48 (m, 4 H), 2.34 (t,  $J = 7.6$  Hz, 4 H), 1.41 (m, 4 H), 0.84 (t,  $J = 7.2$  Hz, 6 H); MS (EI)  $m/z$  389 and 391 ( $\text{M}^+ + 1$ ).

**Example 6****4-(2-{4-[(6-Chloropyridin-3-yl)sulfonyl]piperazin-1-yl}ethyl)morpholine**

Starting material: 4-(2-piperazin-1-ylethyl)morpholine (0.299 g, 1.5 mmol) in a dichloromethane/acetonitrile, (4:1), solvent mixture (3 mL). When the reaction was finished the white solid was filtered off, dissolved in methanol and filtered again. The organic solution was concentrated *in vacuo* to afford 0.541 g (96% yield) of the title compound:  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz)  $\delta$  8.80 (s, 1 H), 8.24 (d,  $J = 8.0$  Hz, 1 H), 7.87 (d,  $J = 8.0$  Hz, 1 H), 3.55 (br s, 4 H), 3.36 (br s, 8 H), 3.01 (br s, 4 H), 2.37 (br s, 4 H); MS (EI)  $m/z$  375 and 377 ( $\text{M}^+ + 1$ ).

**Example 7****1-[(6-Chloropyridin-3-yl)sulfonyl]-4-(2-pyrrolidin-1-ylethyl)piperazine**

Starting material: 1-(2-pyrrolidin-1-ylethyl)piperazine (0.275 g, 1.5 mmol). Yield: 78% of the title compound was obtained without chromatography:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  8.71 (d,  $J = 2.4$  Hz, 1 H), 7.96 (dd,  $J = 8.0, 2.4$  Hz, 1 H), 7.50 (d,  $J = 8.0$  Hz, 1 H), 3.15 (br s, 6 H), 3.00 (br s, 2 H), 2.80 (m, 4 H), 2.61 (t,  $J = 4.8$  Hz, 4 H), 2.02 (m, 4 H); MS (EI)  $m/z$  359 and 361 ( $\text{M}^+ + 1$ ).

**Example 8****1-[(6-Chloropyridin-3-yl)sulfonyl]-4-(2-methoxyethyl)piperazine**

Starting material: 1-(2-methoxyethyl)piperazine (0.216 g, 1.5 mmol). The white solid was filtered off. Yield 92%:  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz)  $\delta$  8.80 (s, 1 H), 8.25 (d,  $J = 8.0$  Hz, 1 H), 7.88 (d,  $J = 8.0$  Hz, 1 H), 3.47 (br s, 2 H), 3.27 (s, 2 H), 3.23 (s, 3 H), 3.08 (br s, 2 H), 3.01 (br s, 4 H), 2.38 (br s, 2 H); MS (EI)  $m/z$  320 and 322 ( $\text{M}^+ + 1$ ).

**Example 9****6-Chloro-*N*-(2-pyrrolidin-1-ylethyl)pyridine-3-sulfonamide**

Starting material: 2-pyrrolidin-1-ylethylamine. Purification on a silica gel column using  
ethyl acetate/triethylamine, (9:1), as the eluent gave the title compound in 58% yield: <sup>1</sup>H  
NMR (CDCl<sub>3</sub>, 400 MHz) δ 8.79 (d, *J* = 2 Hz, 1 H), 8.05 (dd, *J* = 8, 3 Hz, 1 H), 7.42 (d, *J* =  
9 Hz, 1 H), 3.00 (app. t, *J* = 6 Hz, 2 H), 2.50 (app. t, *J* = 6 Hz, 2 H), 2.33 (m, 4 H), 1.67 (m,  
4 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 155.7, 148.8, 137.8, 136.1, 125.0, 54.1, 53.9, 41.6,  
23.9; MS (TSP) *m/z* 290 (*M*<sup>+</sup>+1).

**Example 10****(2-{4-[(6-Chloropyridin-3-yl)sulfonyl]piperazin-1-yl}ethyl)dimethylamine**

To a solution of *N,N*-dimethyl-*N*-(2-piperazin-1-ylethyl)amine (0.80 g, 5.0 mmol) and  
triethylamine (1.0 g, 10 mmol) in dichloromethane (7 mL) was added 6-chloropyridine-3-  
sulfonyl chloride (1.0 g, 5.0 mmol; described in: Naegeli et al. *Helv. Chim. Acta*, **1938**, *21*,  
1746, 1750) in dichloromethane (3 mL) at room temperature. After stirring over night at  
room temperature the solvent was removed *in vacuo*, the residue was partitioned between  
aqueous sodium hydroxide (2 M), diethyl ether (3x15 mL), and dichloromethane (3x15  
mL). The combined extracts were dried (MgSO<sub>4</sub>), and the solvents were removed *in vacuo*  
to afford 1.3 g of the crude product. The residue was purified on a silica gel column using  
acetonitrile/triethylamine, (90:10), as the eluent to afford 1.0 g (60% yield) of title  
compound: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 8.73 (d, *J* = 2 Hz, 1 H), 7.95 (dd, *J* = 8, 2 Hz, 1  
H), 7.48 (d, *J* = 8 Hz, 1 H), 3.08 (t, *J* = 5 Hz, 4 H), 2.56 (t, *J* = 5 Hz, 4 H), 2.47 (t, *J* = 7 Hz,  
2 H), 2.35 (t, *J* = 7 Hz, 2 H), 2.19 (s, 3 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 155.8, 148.8,  
137.8, 131.3, 124.6, 56.7, 56.0, 52.4, 45.8, 45.8.

**Example 11****2-Oxo-*N*-(pyridin-2-ylmethyl)indoline-5-carboxamide**

To a *N,N*-dimethylformamide/acetonitrile, (2 mL:10 mL), mixture containing  
ethyldiisopropylamine (0.52 mL, 3 mmol) was added 2-oxoindoline-5-carboxylic acid  
(0.354 g, 2.0 mmol; described in: Sun L. et al. *J. Med. Chem.* **2000**, *43*(14), 2655:), *O*-  
(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (0.77 g, 2.4 mmol)

and 1-hydroxybenzotriazole hydrate (0.324 g, 2.4 mmol) and stirred for 5 min at room temperature. Thereafter, 2-(aminomethyl)pyridine (0.562 g, 5.2 mmol) was added and the resulting reaction mixture was stirred for 90 min followed by addition of a saturated aqueous NaHCO<sub>3</sub> solution (10 mL). The solvents were removed *in vacuo* and 0.364 g (68% yield) of the title product was obtained as a white solid after purification on a silica gel column using chloroform/methanol, (9:1), as the eluent: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 10.66 (s, 1 H), 8.96 (t, *J* = 5.6 Hz, 1 H), 8.55 (d, *J* = 4.4 Hz, 1 H), 7.85 (d, *J* = 8.0 Hz, 1 H), 7.83 (s, 1 H), 7.78 (t, *J* = 7.6 Hz, 1 H), 7.34 (d, *J* = 8.0 Hz, 1 H), 7.29 (t, *J* = 6.4 Hz, 1 H), 6.92 (d, *J* = 8.0 Hz, 1 H), 4.59 (d, *J* = 6.0 Hz, 2 H), 3.58 (s, 2 H); MS (EI) *m/z* 268 (M<sup>+</sup>+1).

The following Examples, 12-15, were prepared as described for Example 11.

#### **Example 12**

##### **2-Oxo-*N*-(2-thienylmethyl)indoline-5-carboxamide**

Starting material: 2-(aminomethyl)thiophene. Purification on a silica gel column using chloroform/methanol, (9:1), as the eluent gave 0.208 g (76% yield) of the title compound: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 10.65 (s, 1 H), 8.96 (t, *J* = 5.6 Hz, 1 H), 7.80 (d, *J* = 7.6 Hz, 1 H), 7.78 (s, 1 H), 7.40 (t, *J* = 4.0 Hz, 1 H), 7.03 (br s, 1 H), 6.99 (dd, *J* = 4.8, 3.6 Hz, 1 H), 6.90 (d, *J* = 8.0 Hz, 1 H), 4.64 (d, *J* = 5.6 Hz, 2 H), 3.57 (s, 2 H); MS (EI) *m/z* 273 (M<sup>+</sup>+1).

#### **Example 13**

##### **2-Oxo-*N*-[2-(2-oxoimidazolidin-1-yl)ethyl]indoline-5-carboxamide**

Starting material: 1-(2-aminoethyl)imidazolidin-2-one (50% solution in isopropyl alcohol).

Yield: 37%: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 10.63 (s, 1 H), 8.38 (m, 1 H), 7.75 (d, *J* = 8.0 Hz, 1 H), 7.73 (s, 1 H), 6.89 (d, *J* = 8.0 Hz, 1 H), 6.31 (s, 1 H), 3.56 (s, 2 H), 3.43 (m, 4 H), 3.24 (m, 4 H); MS (EI) *m/z* 289 (M<sup>+</sup>+1).

#### **Example 14**

***N*-[2-(Acetylamino)ethyl]-2-oxoindoline-5-carboxamide**

Starting material: *N*-(2-aminoethyl)acetamide. The crude product was purified on a silica gel column using chloroform/methanol/triethylamine, (60:10:1), as the eluent, and was further purified by stirring in acetonitrile (3 mL) for 10 min followed by filtration and drying. Yield: 29% of a pink solid:  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  10.63 (s, 1 H), 8.36 (t,  $J = 5.2$  Hz, 1 H), 7.98 (br s, 1 H), 7.76 (d,  $J = 7.6$  Hz, 1 H), 7.74 (s, 1 H), 6.89 (d,  $J = 8.0$  Hz, 1 H), 3.56 (s, 2 H), 3.31 (m, 2 H), 3.22 (m, 2 H), 1.84 (s, 3 H); MS (EI)  $m/z$  262 ( $M^+ + 1$ ).

### **Example 15**

#### ***N*-(3-Methoxypropyl)-2-oxoindoline-5-carboxamide**

Starting material: 3-methoxypropylamine. Yield: 78% of a white solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  7.68 (s, 1 H), 7.65 (d,  $J = 8.0$  Hz, 2 H), 6.89 (d,  $J = 8.0$  Hz, 1 H), 6.82 (br s, 1 H), 3.58 (m, 6 H), 3.39 (s, 3 H), 1.89 (m, 2 H); MS (EI)  $m/z$  249 ( $M^+ + 1$ ).

### **Example 16**

#### **2-Oxoindoline-5-carboxamide**

A solution of 2-oxoindoline-5-carbonitrile (2.4 g, 15 mmol) in sulphuric acid (85%, 16 mL) was heated at 80 °C for 6 h and then allowed to reach room temperature over night. The mixture was poured into an ice/water mixture and the pH was adjusted to 5 with an aqueous sodium hydroxide solution (50%). The solid product was collected by filtration, washed with water, and dried *in vacuo* at 60 °C over night to afford 2.2 g (83% yield):  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  10.63 (s, 1 H), 7.88-7.72 (m, 3 H), 7.23-7.11 (br s, 1 H), 6.88 (d,  $J = 8$  Hz, 1 H), 3.56 (s, 2 H).

### **Example 17**

#### **2-Oxoindoline-6-carboxamide**

The title compound was prepared as described for Example 16 using 2-oxoindoline-6-carbonitrile (1.2 g, 7.6 mmol) to afford 1.0 g (75% yield) of title compound:  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  10.51 (s, 1 H), 7.91 (br s, 1 H), 7.46 (d,  $J = 8$  Hz, 1 H), 7.31-7.22 (m, 3 H), 3.51 (s, 2 H).



**Example 18****6-Bromo-5-(chloroacetyl)-1,3-dihydro-2H-indol-2-one**

Chloroacetyl chloride (0.65 mL, 8.2 mmol) was added to a cooled (0 °C) suspension of 6-bromooxindol (0.825 g, 3.9 mmol) and aluminium chloride (1.82 g, 13.6 mmol) in 1,2-dichloroethane (8 mL). The resulting mixture was stirred at 0 °C for 20 min and at 50 °C for 17 h. The mixture was cooled to room temperature and was then poured on ice. The formed solid was filtered off, washed with water, and dried *in vacuo* to give 1.10 g (99% yield) of the title compound: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 7.69 (s, 1 H), 7.09 (s, 1 H), 4.97 (s, 2 H), 3.52 (s, 2 H).

**Example 19****6-Bromo-2-oxoindoline-5-carboxylic acid**

A mixture of 6-bromo-5-(chloroacetyl)-1,3-dihydro-2H-indol-2-one (1.11 g, 3.85 mmol) and pyridine (8.0 mL) was heated at 90 °C for 2.5 h. The formed precipitate was filtered off and washed with ethanol. Aqueous sodium hydroxide (10.0 mL, 2.5 M) was added and the resulting mixture was heated at 80 °C for 2 h to give a dark red solution. The reaction mixture was acidified using aqueous hydrochloric acid (5.0 M). The dark red precipitate was filtered off, washed with hydrochloric acid (0.1 M), and dried *in vacuo* to give 0.742 g (75% yield) of the title compound: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 12.94 (br s, 1 H), 10.69 (s, 1 H), 7.66 (s, 1 H), 7.04 (s, 1 H), 3.49 (s, 2 H); MS (ES) *m/z* 254 and 256 (M<sup>-1</sup>).

**Example 20****6-Bromo-N-methyl-2-oxoindoline-5-carboxamide**

Methylamine (0.75 mL, 2.0 M in tetrahydrofuran) was added to a stirred solution of 6-bromo-2-oxoindoline-5-carboxylic acid (0.246 g, 0.96 mmol), *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (0.369 g, 1.15 mmol), 1-hydroxybenzotriazole hydrate (0.176 g, 1.15 mmol), and diisopropylethylamine (0.55 mL, 3.16 mmol) in dry *N,N*-dimethylformamide (4 mL) under an atmosphere of nitrogen. The resulting mixture was stirred at room temperature for 1.5 h. An aqueous solution of sodium bicarbonate was added and the solvent was evaporated. The resulting residue was purified on a silica gel column using dichloromethane/methanol, (9:1), as the eluent to give 0.125 g (48% yield)

of the title compound:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  7.27 (s, 1 H), 7.11 (s, 1 H), 3.20 (m, 2 H), 3.09 (s, 3 H); MS (ES)  $m/z$  269 and 271 ( $\text{M}^+ + 1$ ).

The following Examples, 21-26, were prepared as described for Example 20.

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**Example 21****6-Bromo-*N*-isopropyl-2-oxoindoline-5-carboxamide**

Starting material: isopropylamine. Yield: 63%; MS (ES)  $m/z$  297 and 299 ( $\text{M}^+ + 1$ ).

10 **Example 22****6-Bromo-*N*-(2-methoxyethyl)-2-oxoindoline-5-carboxamide**

Starting material: 2-methoxyethylamine. Yield: 91%;  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ , 400 MHz)  $\delta$  7.19 (s, 1 H), 6.97 (s, 1 H), 3.46 (s, 2 H), 3.42 (m, 2 H), 3.34 (m, 2 H), 3.26 (s, 3 H); MS (ES)  $m/z$  311 and 313 ( $\text{M}^+ - 1$ ).

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**Example 23****6-Bromo-2-oxo-*N*-(tetrahydrofuran-2-ylmethyl)indoline-5-carboxamide**

Starting material: tetrahydrofurfurylamine. Yield: 33%.

20 **Example 24****6-Bromo-2-oxo-*N*-(2-pyrrolidin-1-ylethyl)indoline-5-carboxamide**

Starting material: 1-(2-aminoethyl)pyrrolidine. Yield: 69%; MS (ES)  $m/z$  352 and 354 ( $\text{M}^+ + 1$ ).

25 **Example 25*****N*-Methyl-2-oxoindoline-5-carboxamide**

Starting material: methylamine. Yield: 45%;  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ , 400 MHz)  $\delta$  10.62 (s, 1 H), 8.28 (m, 1 H), 7.71 (m, 1 H), 7.70 (s, 1 H), 6.85 (d,  $J = 8$  Hz, 1 H), 3.53 (s, 2 H), 2.75 (d,  $J = 4$  Hz, 3 H);  $^{13}\text{C}$  NMR ( $\text{DMSO-d}_6$ , 100 MHz)  $\delta$  176.7, 166.4, 146.3, 127.5, 127.2, 125.7, 123.3, 108.4, 35.6, 26.3; MS (ES)  $m/z$  191 ( $\text{M}^+ + 1$ ).

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**Example 26**

***N*-[3-(Dimethylamino)propyl]-2-oxoindoline-5-carboxamide**

Starting material: *N,N*-dimethylpropanediamine. Yield: 63%:  $^1\text{H}$  NMR (DMSO- $\text{d}_6$ , 400 MHz)  $\delta$  7.69 (m, 2 H), 6.83 (d,  $J = 9$  Hz, 1 H), 3.51 (s, 2 H), 3.24 (m, 2 H), 2.31 (m, 2 H), 2.18 (s, 6 H), 1.64 (m, 2 H); MS (ES)  $m/z$  262 ( $\text{M}^+ + 1$ ).

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**Example 27*****N*-(2-Methoxybenzyl)-2-oxoindoline-5-carboxamide**

To a solution of 2-oxoindoline-5-carboxylic acid (0.200 g, 1.12 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.477 g, 2.47 mmol),  
10 diisopropylethylamine (0.586 mL, 3.37 mmol) and catalytic amount of *N,N*-dimethylaminopyridine in *N,N*-dimethylformamide/acteonitrile (1:1, 4 mL) was added 2-methoxybenzylamine (0.295 mL, 2.26 mmol) and the reaction mixture stirred at room temperature for 1 h. The solvent was evaporated and the crude material was purified on a short silica gel column using dichloromethane containing 5% methanol as the eluent. This  
15 was followed by triturating from ethyl acetate to give 0.10 g (33% yield) of the yellow title compound:  $^1\text{H}$  NMR (DMSO- $\text{d}_6$ , 400 MHz)  $\delta$  10.60 (br s, 1 H), 8.65 (t,  $J = 6$  Hz, 1 H), 7.79-7.77 (m, 2 H), 7.21 (t,  $J = 8$  Hz, 1 H), 7.15 (d,  $J = 8$  Hz, 1 H), 6.98 (d,  $J = 8$  Hz, 1 H), 6.90-6.84 (m, 2 H), 4.42 (d,  $J = 6$  Hz, 2 H), 3.81 (s, 3 H), 3.53 (s, 2 H); MS (ES)  $m/z$  297 ( $\text{M}^+ + 1$ ),  $m/z$  295 ( $\text{M}^- - 1$ ).

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The following Examples, 28-30, were prepared as described for Example 27.

**Example 28*****N*-(3-Methoxybenzyl)-2-oxoindoline-5-carboxamide**

25 Starting material: 3-methoxybenzylamine. Yield: 28% of the yellow title compound:  $^1\text{H}$  NMR (DMSO- $\text{d}_6$ , 400 MHz)  $\delta$  10.60 (s, 1 H), 8.83 (t,  $J = 6$  Hz, 1 H), 7.77-7.75 (m, 2 H), 7.24 (t,  $J = 8$  Hz, 1 H), 6.85 (t,  $J = 2$  Hz), 6.80 (m, 1 H), 4.40 (d,  $J = 6$  Hz, 2 H), 3.71 (s, 3 H), 3.52 (s, 2 H).

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**Example 29*****N*-(4-Methoxybenzyl)-2-oxoindoline-5-carboxamide**

Starting material: 4-methoxybenzylamine. Yield: 40%:  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  10.59 (s, 1 H), 8.77 (t,  $J$  = 6 Hz, 1 H), 7.75 (m, 2 H), 7.22 (d,  $J$  = 10 Hz, 2 H), 6.87-6.83 (m, 3 H), 4.37 (d,  $J$  = 5 Hz, 2 H), 3.71 (s, 3 H), 3.51 (br s, 2 H); MS (ES)  $m/z$  297 ( $M^+$ +1),  $m/z$  295 ( $M^-$ -1).

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### **Example 30**

#### **2-Oxo-*N*-(tetrahydro-2*H*-pyran-4-yl)indoline-5-carboxamide**

Starting material: tetrahydropyran-4-ylamine. Yield: 18%:  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  10.58 (s, 1 H), 8.11 (d,  $J$  = 11 Hz, 1 H), 7.73 (m, 2 H), 6.84 (d,  $J$  = 11 Hz, 1 H), 3.95 (m, 1 H), 3.86 (d,  $J$  = 11 Hz, 2 H), 3.51 (s, 2 H), 3.36 (t,  $J$  = 11 Hz, 2 H), 1.72 (d,  $J$  = 11 Hz, 2 H), 1.60-1.51 (m, 2 H).

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### **Example 31**

#### ***N*-Benzyl-2-oxoindoline-5-carboxamide**

2-Oxoindoline-5-carboxylic acid (0.214 g, 1.21 mmol), *O*-(benzotriazol-1-yl)-*N*, *N*, *N'*, *N'*-tetramethyluronium tetrafluoroborate (0.462 g, 1.44 mmol), 1-hydroxybenzotriazole hydrate (0.194 g, 1.44 mmol) and *N,N*-diisopropylethylamine (0.3 mL, 1.71 mmol) were suspended in a mixture of acetonitrile (4 mL) and *N,N*-dimethylformamide (1 mL) and stirred at room temperature for 30 min. Benzylamine (0.155 g, 1.45 mmol) was added and stirring was continued for 12 h. The solvent was removed *in vacuo* and the residue was separated between chloroform and a saturated aqueous sodium hydrogen carbonate solution. The aqueous layer was extracted with chloroform (3x30 mL). The combined organic layers were dried over sodium sulfate. Filtration and removal of the solvent *in vacuo* yielded the crude product which was purified on a silica gel column using a gradient chloroform/methanol, (100:1 to 1:1), as the eluent to give 0.104 g (30% yield) of the title compound as a solid:  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  10.60 (s, 1 H), 8.85 (m, 1 H), 7.77 (m, 2 H), 7.29 (m, 4 H), 7.21 (m, 1 H), 6.85 (d,  $J$  = 11 Hz, 1 H), 4.45 (d,  $J$  = 6 Hz, 2 H), 3.52 (s, 2 H); MS (ES)  $m/z$  267 ( $M^+$ +1).

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### **Example 32**

#### ***N*-(2-Methoxyethyl)-2-oxoindoline-5-carboxamide**

2-Oxoindoline-5-carboxylic acid (0.470 g, 2.66 mmol), *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (1.010 g, 3.15 mmol), 1-hydroxybenzotriazole hydrate (0.417 g, 3.09 mmol) and *N,N*-diisopropylethylamine (0.7 mL, 4.0 mmol) were suspended in acetonitrile/*N,N*-dimethylformamide, (10 mL:2 mL), and stirred at room temperature for 30 min. 2-Methoxyethanamine (0.516 g, 6.88 mmol) was added and stirring was continued for 2 h. Saturated aqueous sodium hydrogencarbonate was added (10 mL) and the solvents were removed *in vacuo*. The residue was purified on a silica gel column using a gradient chloroform/methanol, (100:1 to 1:1), as the eluent to give 0.355 g (57% yield) of the title compound as a solid: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ 10.59 (s, 1 H), 8.31 (m, 1 H), 7.72 (d, *J* = 7 Hz, 1 H), 7.71 (s, 1 H), 6.83 (d, *J* = 8 Hz, 1 H), 3.51 (s, 2 H), 3.42 (m, 2 H), 3.39 (m, 2 H), 3.24 (s, 3 H); MS (ES) *m/z* 235 (*M*<sup>+</sup>+1).

The following Examples, 33-35, were prepared as described for Example 32.

#### **Example 33**

##### **2-Oxo-*N*-propylindoline-5-carboxamide**

Starting material: propylamine. Yield: 11% as a solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 7.72 (d, *J* = 8 Hz, 1 H), 7.71 (s, 1 H), 6.92 (d, *J* = 8 Hz, 1 H), 3.57 (s, 1 H), 3.31 (m, 2 H), 1.62 (sext, *J* = 7 Hz, 2 H), 0.96 (t, *J* = 4 Hz, 3 H); MS (ES) *m/z* 219 (*M*<sup>+</sup>+1).

#### **Example 34**

##### ***N*-[2-(Dimethylamino)ethyl]-2-oxoindoline-5-carboxamide**

Starting material: *N,N*-dimethylethane-1,2-diamine. The residue was purified on a silica gel column using a gradient chloroform/methanol mixtures, (100:1 to 1:1 and 3% triethylamine), as the eluent. The residue was purified by preparative HPLC, (Xterra column (19x300 mm) with 0.05 M NH<sub>4</sub>OAc buffert/acetonitrile, (90:10-30:70), as the eluent) to give the title compound in 18% yield: <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 7.75 (m, 2 H), 6.93 (d, *J* = 8 Hz, 1 H), 3.70 (t, *J* = 6 Hz, 2 H), 3.17 (t, *J* = 6 Hz, 2 H), 2.77 (m, 6 H); MS (ES) *m/z* 248 (*M*<sup>+</sup>+1).

#### **Example 35**

##### ***N*-(2-Cyanoethyl)-2-oxoindoline-5-carboxamide**

Starting material: 3-aminopropanenitrile. Work up: to the reaction mixture, methanol (3 mL) was added and the solvents were removed *in vacuo*. The residue was purified by re-crystallization from acetonitrile, and dried at 45 °C *in vacuo* to afford the title compound in 65% yield: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 10.63 (s, 1 H), 8.65 (t, *J* = 6 Hz, 1 H), 7.77-7.70 (m, 2 H), 6.87 (d, *J* = 8 Hz, 1 H), 3.54 (s, 2 H), 3.47 (q, *J* = 12, 6 Hz, 2 H), 2.75 (t, *J* = 6 Hz, 2 H); MS (ES) *m/z* 230 (*M*<sup>+</sup>+1).

### **Example 36**

#### **4-[(6-Chloro-1-oxidopyridin-3-yl)methyl]morpholine**

A mixture of 2-chloro-5-(chloromethyl)pyridine 1-oxide (1.16 g, 6.52 mmol; described in: Tilley, J. W. et al, *J. Heterocyclic Chem.* **1979**, 16, 333), morpholine (1.14 g, 13.0 mmol), and potassium carbonate (0.90 g, 6.52 mmol) in acetonitrile (30 mL) was stirred at room temperature for 72 h. The solvent was removed *in vacuo* and the residue was purified on a silica gel column using chloroform/ethanol, (9:1), as the eluent affording 1.2 g (81% yield) of the title compound as a colorless solid: mp 72-74 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 8.34 (s, 1 H), 7.39 (d, *J* = 8 Hz, 1 H), 7.16 (dd, *J* = 8, 2 Hz, 1 H), 3.65 (t, *J* = 5 Hz, 4 H), 3.40 (s, 2 H), 2.40 (t, *J* = 4 Hz, 4 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ 140.4, 135.9, 126.6, 126.6, 66.8, 59.2, 53.4; MS (ESP) *m/z* 229 (*M*<sup>+</sup>+1).

### **Example 37**

#### **4-[(6-Chloropyridin-3-yl)sulfonyl]morpholine**

A solution of triethylamine (0.27 mL, 1.94 mmol) and morpholine (0.085 mL, 0.97 mmol) in dry dichloromethane (2 mL) was added to a stirred suspension of 6-chloropyridine-3-sulfonyl chloride (0.204 g, 0.96 mmol; described in: Naegeli, C. et al. *Helv. Chim. Acta.* **1938**, 21, 1746-1750) in dry dichloromethane (1 mL). The resulting clear solution was stirred at room temperature for 20 min. The solvent was evaporated and the residue was purified on a silica gel column using dichloromethane/methanol, (97:3), as the eluent to give 0.176 g (70% yield) of the title compound: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 8.75 (dd, *J* = 3, 1 Hz, 1 H), 8.18 (dd, *J* = 8, 3 Hz, 1 H), 7.82 (dd, *J* = 8, 1 Hz, 1 H), 3.63 (m, 4 H), 2.96 (m, 4 H).

**Example 38*****N*-[(6-Chloro-1-oxidopyridin-3-yl)methyl]-*N*-ethylethanamine**

2-Chloro-5-chloromethylpyridine 1-oxide (1.78 g, 10.0 mmol; described in: Tilley, J. W. et al, *J. Heterocyclic Chem.* **1979**, *16*, 333), diethyl amine (1.46 g, 20.0 mmol), and potassium carbonate (1.38 g, 10.0 mmol) were mixed in acetonitrile (50 mL) at room temperature. The mixture was stirred for 16 h, the solvent was removed *in vacuo*, and the residue was purified on a silica gel column using chloroform/methanol, (9:1), as the eluent to give 1.90 g (88% yield) of the title compound as a pale orange oil: MS (EI) *m/z* 215 and 217 ( $M^+ + 1$ ).

**Example 39****1-[(6-Chloro-1-oxidopyridin-3-yl)methyl]-4-methylpiperazine**

A mixture of 2-chloro-5-(chloromethyl)pyridine 1-oxide (0.5 g, 2.8 mmol; described in: Tilley, J. W. et al, *J. Heterocyclic Chem.* **1979**, *16*, 333), 1-methylpiperazine (0.34 g, 3.37 mmol), and potassium carbonate (0.78 g, 5.62 mmol) in acetonitrile (5 mL) was stirred at room temperature for 13 h. The solvent was removed *in vacuo* and the residue was purified on a silica gel column using a gradient dichloromethane/methanol, (100:1 to 2:1), as the eluent affording 0.57 g (84% yield) of the title compound as a colorless solid:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  8.34 (s, 1 H), 7.38 (d,  $J = 8$  Hz, 1 H), 7.12 (d,  $J = 8$  Hz, 1 H), 3.42 (s, 2 H), 2.52 (s, 8 H), 2.34 (m, 3 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  140.6, 140.6, 136.3, 126.7, 58.9, 55.0, 52.6, 45.8; MS (ESP) *m/z* 242 ( $M^+ + 1$ ).

The following Examples, 40–41, were prepared as described for Example 39.

**Example 40****1-[(6-Chloro-1-oxidopyridin-3-yl)methyl]piperidine**

Starting material: piperidine (0.29 g, 3.37 mmol). Yield: 0.47 g, 74%:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  8.30 (s, 1 H), 7.35 (d,  $J = 8$  Hz, 1 H), 7.13 (d,  $J = 8$  Hz, 1 H), 3.32 (s, 2 H), 2.29 (d,  $J = 4$  Hz, 4 H), 1.49 (m, 4 H), 1.36 (m, 2 H); MS (ESP) *m/z* 227 ( $M^+ + 1$ ).

**Example 41**

**4-[(6-Chloro-1-oxidopyridin-3-yl)methyl]piperazin-2-one**

Starting material: piperazinone (0.75 g, 7.5 mmol). Yield: 1.24 g, 73%:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  8.46 (d,  $J = 1$  Hz, 1 H), 7.70 (d,  $J = 8$  Hz, 1 H), 7.51 (dd,  $J = 8, 2$  Hz, 1 H), 3.62 (s, 2 H), 3.29 (m, 2 H), 3.12 (m, 2 H), 2.67 (m, 2 H); MS (ESP)  $m/z$  242 ( $\text{M}^+ + 1$ ).

5

**Example 42*****N*-{2-[(4-Methylpiperazin-1-yl)sulfonyl]ethyl}-2-oxoindoline-5-carboxamide**

A solution of taurine (2.6 g, 21 mmol) in aqueous sodium hydroxide (1 M, 21 mL) was cooled to 0 °C. Then, under vigorous stirring, a solution of benzyl chloroformate (4.2 g, 25 mmol) in dioxane (10 mL) was poured into the reaction mixture followed by the rapid addition of aqueous sodium hydroxide (1 M, 25 mL). After stirring for 1 h at 0 °C, the reaction mixture was extracted with ethyl acetate (2×100 mL). Evaporation of the aqueous phase *in vacuo* followed by co-evaporation with toluene (2×200 mL) afforded the crude sodium sulfonate salt, which was dried *in vacuo*. The resulting solid material was suspended in benzene (100 mL), and an excess of thionyl chloride (6.0 mL, 83 mmol) was added dropwise. The reaction mixture was stirred for 1 h at 50 °C and then under reflux for 2 h. After cooling, the mixture was concentrated *in vacuo*, dried, suspended in dichloromethane (50 mL), cooled to 0 °C, and treated with a solution of *N*-methylpiperazine (2.3 mL, 21 mmol) in dichloromethane (20 mL). The solution was stirred for 16 h at room temperature, silica (10 g) was added, and the mixture was concentrated to dryness. The resulting solid residue was purified on a silica gel column using heptane/ethyl acetate, (1:1), as the eluent to afford 1 g (14 % yield) of the benzyloxycarbonyl-protected sulfonamide as a colorless oil: MS (ES)  $m/z$  342 ( $\text{M}^+ + 1$ ). The above material was dissolved in methanol (50 mL) and formic acid (5 mL) and hydrogenated over Pd/C (0.40 g) at elevated hydrogen pressure (50 psi) for 16 h. The reaction mixture was filtered through a plug of celite (10 g), the celite was washed with methanol (2×20 mL), the combined filtrates were evaporated to dryness, dissolved in  $\text{H}_2\text{O}$  (20 mL), and re-evaporated. The resulting residue was dissolved in *N,N*-dimethylformamide (5 mL), and added in one portion to the previously prepared suspension of 2-oxoindoline-5-carboxylic acid (0.53 g, 3 mmol), *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (1.1 g, 3.6

30



mmol), 1-hydroxybenzotriazole (0.486 g, 3.6 mmol) and *N,N*-diisopropylethylamine (1.7 g, 12 mmol) in acetonitrile (10 mL) and *N,N*-dimethylformamide (10 mL). The mixture was stirred overnight, the solvents were removed *in vacuo*, and the residue was purified on a silica gel column using chloroform/methanol, (10:1), then chloroform/methanol/ aqueous ammonia, (100:10:1), as the eluent. The semi-solid crude material was again subjected to silica gel chromatography using chloroform/methanol/ aqueous ammonia, (150:10:1), as the eluent to afford 0.20 g (19% yield) the title compound as yellow foam: MS (ES) *m/z* 367 ( $M^+ + 1$ ).

#### 10 **Example 43**

##### **4-{2-[(6-Chloropyrimidin-4-yl)oxy]ethyl}morpholine**

A mixture of 4,6-dichloropyrimidine (1.0 g, 6.7 mmol), *N*-(2-hydroxyethyl)morpholine (0.79 g, 0.60 mmol), and potassium carbonate (2.8 g, 20 mmol) in acetonitrile (5 mL) was stirred at room temperature for 15 h. The solvent was removed *in vacuo* and the residue was purified on a silica gel column using a gradient dichloromethane/methanol, (100:1 to 2:1), as the eluent to give 0.47 g (32% yield) of the yellow title compound:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  8.48 (s, 1 H), 6.72 (s, 1 H), 4.45 (t,  $J = 6$  Hz, 2 H), 3.62 (m, 4 H), 2.46 (m, 4 H) 2.69 (t,  $J = 6$  Hz, 2 H),  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  169.9, 160.5, 157.9, 107.8, 66.7, 64.4; MS (ESP) *m/z* 244 ( $M^+ + 1$ ).

#### 20 **Example 44**

##### ***N*-{2-[(6-Chloropyrimidin-4-yl)oxy]ethyl}-*N*-isopropylpropan-2-amine**

A mixture of 4,6-dichloropyrimidine (0.5 g, 3.4 mmol), 2-(diisopropylamino)ethanol (0.44 g, 3.0 mmol), and cesium carbonate (2.18 g, 6.7 mmol) in butyronitrile (4 mL) was heated in a microwave oven at 180 °C for 20 min. Filtration followed by purification using preparative HPLC (XTerra® PrepMS C8 column 10  $\mu\text{m}$ , 30x150 mm; 0.1 M  $\text{NH}_4\text{OAc}$  buffer/acetonitrile, (80:20-20:80), as the eluent) gave 0.156 g (20% yield) of the title compound: MS (ESP) *m/z* 258 ( $M^+ + 1$ ).

#### 30 **Example 45**

##### **Ethyl 6-(6-cyano-2-hydroxy-1*H*-indol-3-yl)nicotinate**

To a *N,N*-dimethylformamide (6 mL) suspension of sodium hydride (97%, 0.144 g, 6.0 mmol) was added 2-oxoindoline-6-carbonitrile (0.712 g, 4.5 mmol). The formed mixture was stirred for 10 min at room temperature followed by the addition of ethyl 6-chloronicotinate 1-oxide (0.605 g, 3.0 mmol). The resulting reaction mixture was set under N<sub>2</sub> atmosphere and stirred for 2 h at room temperature. The *N,N*-dimethylformamide reaction solution was diluted with a saturated aqueous sodium hydrogen carbonate solution and extracted with chloroform and ethyl acetate. The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The remaining *N,N*-dimethylformamide was removed by co-evaporation with toluene. The residue was dissolved in chloroform (10 mL) and phosphorus trichloride (1.65 g, 12.0 mmol) was added. The reaction mixture was stirred for 30 min at 60 °C and then cooled to room temperature. The mixture was poured into a saturated aqueous sodium hydrogen carbonate solution. The resulting brown precipitate was filtered off and the mother liquor was extracted with chloroform (4x). The organic layers were concentrated *in vacuo* and the residue was combined with the filtrate and was washed with ethyl acetate and diethyl ether to afford 0.55 g (60% yield) of the title compound as a yellow-brown solid: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 8.85 (s, 1 H), 8.06 (s, 1 H), 8.00 (d, *J* = 8.8 Hz, 1 H), 7.75 (d, *J* = 8.0 Hz, 1 H), 7.69 (d, *J* = 8.0 Hz, 1 H), 7.45 (s, 1 H), 7.29 (d, *J* = 8.8 Hz, 1 H), 4.33 (m, 2 H), 1.35 (t, *J* = 7.2 Hz, 3 H); MS (EI) *m/z* 308 (M<sup>+</sup>+1).

#### **Example 46**

##### **Methyl 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxylate**

To a *N,N*-dimethylformamide (10 mL) suspension of sodium hydride (97%, 0.784 g, 32.7 mmol) was added methyl 2-oxoindoline-5-carboxylate (2.34 g, 12.3 mmol). The formed mixture was stirred for 10 min at room temperature followed by the addition of 4-[(6-chloro-1-oxidopyridin-3-yl)methyl]morpholine (1.87 g, 8.2 mmol). The resulting reaction mixture was set under N<sub>2</sub> atmosphere and stirred for 1 h at 135 °C. The *N,N*-dimethylformamide solution was diluted with saturated aqueous sodium hydrogen carbonate (30 mL) and extracted with chloroform, and ethyl acetate (containing 5% methanol). The combined organic phases were concentrated *in vacuo*. The remaining *N,N*-dimethylformamide was removed by co-evaporation with toluene. The residue was dissolved in ethyl acetate/chloroform, (150 mL, 2:1), and phosphorus trichloride (4.5 g, 33

mmol) was added. The reaction mixture was stirred for 1 h at 60 °C, and then cooled to room temperature. The mixture was poured into a saturated aqueous sodium hydrogen carbonate solution followed by extraction of the aqueous phase with chloroform (4x). The combined organic extracts were concentrated *in vacuo*, and the residue was purified on a silica gel column using chloroform/methanol, (10:1), as the eluent to afford 1.05 g (35% yield) of the title compound as a yellow-brown solid: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 10.83 (br s, 1 H), 8.11 (s, 1 H), 8.04 (s, 1 H), 7.91 (d, *J* = 8.0 Hz, 1 H), 7.63 (t, *J* = 8.0 Hz, 2 H), 7.00 (d, *J* = 8.0 Hz, 1 H), 3.87 (s, 3 H), 3.62 (br s, 4 H), 3.41 (s, 2 H), 2.42 (br s, 4 H); MS (EI) *m/z* 368 (M<sup>+</sup>+1).

#### Example 47

##### **Methyl 3-{5-[(diethylamino)methyl]pyridin-2-yl}-2-hydroxy-1*H*-indole-5-carboxylate**

The title compound was prepared according to Example 46 using *N*-[(6-chloro-1-oxidopyridin-3-yl)methyl]-*N*-ethylethanamine (0.950 g, 4.4 mmol). The product was obtained as an orange yellow solid (0.492 g, 32% yield): <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.19 (s, 1 H), 8.05 (s, 1 H), 7.93 (dd, *J* = 8.0, 2.0 Hz, 1 H), 7.92 (d, *J* = 9.6 Hz, 1 H), 7.74 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.10 (d, *J* = 8.4 Hz, 1 H), 3.94 (s, 3 H), 3.81 (br s, 2 H), 2.85 (br s, 4 H), 1.34 (t, *J* = 7.2 Hz, 6 H); MS (EI) *m/z* 354 (M<sup>+</sup>+1).

#### Example 48

##### **Methyl 2-hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxylate**

The title compound was prepared as described for Example 103 using 1-[(6-chloropyridine-3-yl)sulfonyl]-4-methylpiperazine (described in: Thunus. L. *Annales Pharmaceutiques Francaises* 1977, 35, 197-204) and methyl 2-oxoindoline-5-carboxylate to give the title compound in 59% yield, but without the treatment of the base with hydrochloric acid to from the salt: <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz) δ 8.03 (d, *J* = 2 Hz, 1 H), 7.44 (m, 1 H), 7.30 (d, *J* = 8 Hz, 1 H), 7.23 (s, 1 H), 6.82 (d, *J* = 9 Hz, 1 H), 6.70 (d, *J* = 8 Hz, 1 H), 3.93 (m, 2 H), 3.82 (s, 3 H), 3.65 (m, 2 H), 3.28 (m, 2 H), 3.03 (m, 2 H), 2.94 (s, 3 H); MS (TSP) *m/z* 431 (M<sup>+</sup>+1).

#### Example 49

**2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1H-indole-5-carboxylic acid**

To a mixture of 2-hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1H-indole-5-carbonitrile (0.10 g, 0.25 mmol) in water (2 mL) was added 1 M aqueous sodium hydroxide solution (1.3 mL, 1.3 mmol) followed by water (1 mL) in a microwave vial. The mixture was subjected to microwave irradiation for 15 min at 140 °C. The pH was adjusted to 5 with 2 M HCl. The solid product was collected by filtration, washed with diethyl ether, and dried to afford 0.11 g (89% yield) of the title compound: MS (ESP)  $m/z$  417 ( $M^+ + 1$ ).

**Example 50**

**Methyl 3-(4-cyanopyridin-2-yl)-2-hydroxy-1H-indole-5-carboxylate**

The title compound was prepared as described for Example 86 using methyl 2-oxoindoline-5-carboxylate and 2-chloro-5-cyanopyridine, but the reaction mixture was heated to 135 °C for 1 h. The product was purified on a silica gel column using chloroform/methanol, (first 20:1, then 15:1), as the eluent to afford the title compound as a dark-red powder in 20% yield: MS (ES)  $m/z$  294 ( $M^+ + 1$ ).

**END PRODUCTS**

**Example 51**

**2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)carbonyl]pyridin-2-yl}-1H-indole-6-carbonitrile hydrochloride**

To a suspension of sodium hydride (97%, 0.024 g, 1.0 mmol) in *N,N*-dimethylformamide (1.5 mL) was added 2-oxoindoline-6-carbonitrile (0.119 g, 0.75 mmol). The resulting mixture was stirred for 5 min at room temperature and 1-[(6-chloro-1-oxidopyridin-3-yl)carbonyl]-4-methylpiperazine (0.128 g, 0.5 mmol) was added. The resulting reaction mixture was set under an  $N_2$  atmosphere and stirred for 20 h at room temperature. The *N,N*-dimethylformamide reaction solution was diluted with saturated aqueous sodium hydrogen carbonate and sodium chloride (2.0 g) was added followed by extractions with chloroform, ethyl acetate, and tetrahydrofuran. The combined organic extracts were dried ( $Na_2SO_4$ ) and concentrated *in vacuo*. The remaining *N,N*-dimethylformamide was removed by co-evaporation with toluene (1x). The residual oil was dissolved in a chloroform/ethyl

acetate, (5:1, 6 mL), and phosphorus trichloride (0.275 g, 2.0 mmol) was added. The reaction mixture was stirred for 60 min at 60 °C, and was then cooled to room temperature. The mixture was poured into a saturated aqueous sodium hydrogen carbonate solution and sodium chloride (2.0 g) was added followed by extractions with chloroform (4x) and ethyl acetate (2x). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. Purification using preparative HPLC (XTerra® PrepMS C8 column 10 µm, 30x150 mm; 0.1 M NH<sub>4</sub>OAc buffer/acetonitrile, (80:20-20:80), as the eluent) gave 0.028 g (15% yield) of the title compound as the base. The base (0.025 g, 0.069 mmol) was dissolved in chloroform/methanol, (1:1), and treated with HCl in diethyl ether (1 M) at 0 °C. The resulting yellow crystals were collected by filtration and washed with diethyl ether to obtain 0.020 g (70% yield) of the title compound: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 10.61 (br s, 1 H), 8.41 (s, 1 H), 7.93 (br s, 1 H), 7.80 (br s, 2 H), 7.30 (br s, 1 H), 7.15 (br s, 1 H), 3.58 (br s, 4 H), 2.40 (br s, 4 H), 2.25 (s, 3 H); MS (EI) *m/z* 362 (M<sup>+</sup>+1).

#### **Example 52**

##### **6-(6-Cyano-2-hydroxy-1*H*-indol-3-yl)-*N*-(2-morpholin-4-ylethyl)nicotinamide hydrochloride**

A suspension of ethyl 6-(6-cyano-2-hydroxy-1*H*-indol-3-yl)nicotinate (0.092 g, 0.3 mmol) and 4-(2-aminoethyl)morpholine (0.098 g, 0.75 mmol) in benzene (4.0 mL) was prepared at room temperature and was set under an N<sub>2</sub> atmosphere. To the suspension, trimethylaluminum (2 M solution in hexane, 0.6 mL, 1.2 mmol) was added via syringe at 0 °C. After 5 min, the reaction mixture was heated to 70 °C and was stirred for another 16 h. The mixture was cooled to room temperature, poured into a saturated aqueous sodium hydrogen carbonate solution (10 mL), and extracted with chloroform. The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residue was purified on a silica gel column using chloroform/methanol/triethylamine, (100:20:1), as the eluent to afford 0.020 g (17% yield) of the title compound as the base. The base (0.020 g, 0.005 mmol) was dissolved in chloroform/methanol, (1:1), and treated with HCl in diethyl ether (1 M) at 0 °C followed by addition of diethyl ether. The resulting yellow crystals were collected by filtration and washed with diethyl ether to obtain 0.020 g (87% yield) of the title compound: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 10.92 (s, 2 H), 9.13 (t, *J* = 4.8 Hz, 1 H), 8.81 (s, 1 H), 8.36 (d, *J* = 9.2 Hz, 1 H), 7.86 (d, *J* = 9.2 Hz, 1 H), 7.80 (d, *J* = 8.0 Hz, 1 H),

7.38 (d,  $J = 8.0$  Hz, 1 H), 7.23 (s, 1 H), 4.34 (d,  $J = 11.6$  Hz, 2 H), 3.86 (t,  $J = 12.0$  Hz, 2 H), 3.73 (m, 2 H), 3.61 (d,  $J = 11.6$  Hz, 2 H), 3.35 (m, 2 H), 3.17 (m, 2 H); MS (EI)  $m/z$  392 ( $M^+ + 1$ ).

5 The following Examples, 53 and 54, were prepared as described for Example 52.

#### **Example 53**

##### **6-(6-Cyano-2-hydroxy-1*H*-indol-3-yl)-*N*-methyl-*N*-(2-pyrrolidin-1-ylethyl)nicotinamide hydrochloride**

10 Starting material: methyl-(2-pyrrolidin-1-ylethyl)amine (0.096 g, 0.75 mmol, 2.5 equiv.; described in: Krapcho J. et al. *J. Am. Chem. Soc.* **1955**, 77, 3632-3634). The crude product was purified on a silica gel column using chloroform/methanol/triethylamine, (100:33:1), as the eluent to give 0.056 g (50% yield) of the title compound as the base. The hydrochloride salt was obtained (0.040 g, 62% yield) as a yellow solid:  $^1\text{H}$  NMR (DMSO-  
15  $\text{d}_6$ , 400 MHz)  $\delta$  10.89 (s, 1 H), 9.97 (br s, 1 H), 8.51 (s, 1 H), 8.05 (d,  $J = 8.8$  Hz, 1 H), 7.85 (d,  $J = 8.8$  Hz, 1 H), 7.75 (d,  $J = 8.0$  Hz, 1 H), 7.39 (d,  $J = 8.0$  Hz, 1 H), 7.24 (s, 1 H), 3.81 (m, 6 H), 3.47 (m, 2 H), 3.12 (br s, 3 H), 2.06 (m, 2 H), 1.93 (m, 2 H); MS (EI)  $m/z$  390 ( $M^+ + 1$ ).

#### **Example 54**

##### **6-(6-Cyano-2-hydroxy-1*H*-indol-3-yl)-*N*-(2-(dimethylamino)ethyl)-*N*-methylnicotinamide hydrochloride**

20 Starting material: *N,N,N'*-trimethylethane-1,2-diamine (2.5 equiv.). The crude product was dissolved in chloroform/methanol, (1:1), and the insoluble material was filtered off followed by concentration *in vacuo*. Yield: 85% of the title compound:  $^1\text{H}$  NMR (DMSO-  
25  $\text{d}_6$ , 400 MHz)  $\delta$  10.90 (s, 1 H), 9.97 (br s, 1 H), 8.52 (s, 1 H), 8.05 (d,  $J = 7.2$  Hz, 1 H), 7.85 (d,  $J = 7.2$  Hz, 1 H), 7.75 (d,  $J = 8.0$  Hz, 1 H), 7.39 (d,  $J = 8.0$  Hz, 1 H), 7.24 (s, 1 H), 3.83 (br s, 9 H), 3.40 (m, 2 H), 2.87 (m, 2 H); MS (EI)  $m/z$  364 ( $M^+ + 1$ ).

#### **Example 55**

##### **6-(6-Cyano-2-hydroxy-1*H*-indol-3-yl)-*N*-(2-pyrrolidin-1-ylethyl)pyridine-3-sulfonamide hydrochloride**

To a suspension of sodium hydride (97%, 0.036 g, 1.5 mmol) in 1-methyl-2-pyrrolidinone (2 mL) was added 2-oxoindoline-6-carbonitrile (0.119 g, 0.75 mmol). The formed mixture was stirred for 5 min at room temperature and 6-chloro-*N*-(2-pyrrolidin-1-ylethyl)pyridine-3-sulfonamide (0.145 g, 0.5 mmol) was added. The resulting reaction mixture was set  
5 under an N<sub>2</sub> atmosphere and stirred for 1 h at 90 °C. Methanol (0.4 mL) was added and the solvents were removed *in vacuo*. The crude product was purified by preparative HPLC purification (XTerra® PrepMS C8 column 10 µm, 30x150 mm; 0.1 M NH<sub>4</sub>OAc buffer/acetonitrile, (80:20 to 40:60), as a eluent gradient). The collected product was stirred for 16 h in methanol/ethyl acetate, (5:1 mL), and the brownish red solid was  
10 collected by filtration affording 0.056 g (27% yield) of the title compound as the base. The base (0.046 g, 0.11 mmol) was dissolved in chloroform/methanol, (1:1), and treated with HCl in diethyl ether (1 M) at 0 °C. The resulting brownish red crystals were collected by filtration and washed with diethyl ether to obtain 0.022 g (40% yield) of the title compound: <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz) δ 8.63 (s, 1 H), 8.10 (d, *J* = 9.2 Hz, 1 H), 7.99 (d, *J* = 8.4 Hz, 1 H), 7.80 (dd, *J* = 9.2, 2.4 Hz, 1 H), 7.22 (s, 1 H), 7.21 (dd, *J* = 8.0, 1.6 Hz, 1 H)  
15 2.91 (t, *J* = 6.8 Hz, 2 H), 2.51 (m, 6 H), 1.61 (br s, 4 H); MS (EI) *m/z* 412 (M<sup>+</sup>+1).

### **Example 56**

#### **2-Hydroxy-3-[5-(piperazine-1-sulfonyl)pyridin-2-yl]-1*H*-indole-6-carbonitrile hydrochloride**

  
20

To a suspension of sodium hydride (97%, 0.024 g, 1.0 mmol) in 1-methyl-2-pyrrolidinone (2 mL) was added 2-oxoindoline-6-carbonitrile (0.119 g, 0.75 mmol). The formed mixture was stirred for 5 min at room temperature and *tert*-butyl 4-[(6-chloropyridin-3-yl)sulfonyl]piperazine-1-carboxylate (0.181 g, 0.5 mmol) was added. The resulting  
25 reaction mixture was set under an N<sub>2</sub> atmosphere and stirred for 1 h at 90 °C. Methanol (0.5 mL) was added to the mixture and the solvents were removed *in vacuo*. The crude product was dissolved in methanol (5 mL) and HCl in diethyl ether (4 M, 2.5 mL, 10 mmol) was added followed by reflux for 3 h. From the cooled solution the formed yellow precipitate was collected by filtration and dried to give 0.209 g (92% yield) of the title  
30 compound: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ 11.08 (s, 1 H), 9.10 (br s, 2 H), 8.67 (s, 1 H), 7.89 (s, 2 H), 7.78 (d, *J* = 8.0 Hz, 1 H), 7.44 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.28 (d, *J* = 1.2 Hz, 1 H) 3.31 (br s, 4 H), 3.25 (br s, 4 H); MS (EI) *m/z* 384 (M<sup>+</sup>+1).

**Example 57****3-[5-({4-[2-(Dipropylamino)ethyl]piperazin-1-yl)sulfonyl}pyridin-2-yl)-2-hydroxy-1H-indole-6-carbonitrile hydrochloride**

5 To a suspension of sodium hydride (97%, 0.024 g, 1.0 mmol) in 1-methyl-2-pyrrolidinone (1.5 mL) was added (2-{4-[(6-chloropyridin-3-yl)sulfonyl]piperazin-1-yl}ethyl)dipropylamine (0.194 g, 0.5 mmol) at room temperature followed by addition of 2-oxoindoline-6-carbonitrile (0.095 g, 0.6 mmol). The formed mixture was stirred for 5 min under an N<sub>2</sub> atmosphere and stirred for 1 h at 90 °C. The cooled solution was poured  
10 into a cold saturated aqueous sodium hydrogen carbonate solution and the resulting precipitate was collected by filtration. The crude product was purified on a silica gel column using chloroform/methanol/triethylamine, (100:80:1), as the eluent to give 0.130 g (51% yield) of the title compound as the base. The base (0.127 g, 0.25 mmol) was dissolved in chloroform/methanol, (1:1), and treated with HCl in diethyl ether (1 M) at 0  
15 °C. The resulting orange crystals were collected by filtration and washed with diethyl ether to obtain 0.125 g (86% yield) of the title compound: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 11.07 (s, 1 H), 8.67 (s, 1 H), 7.89 (s, 2 H), 7.78 (d, *J* = 8.0 Hz, 1 H), 7.44 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.28 (d, *J* = 1.2 Hz, 1 H), 4.04 (br s, 10 H), 3.05 (br s, 6 H), 1.69 (br s, 4 H), 0.91 (t, *J* = 7.2 Hz, 6 H); MS (EI) *m/z* 511 (M<sup>+</sup>+1).

20

The following Examples, 58-61, were prepared as described for Example 57.

**Example 58****2-Hydroxy-3-(5-{[4-(2-morpholin-4-ylethyl)piperazin-1-yl)sulfonyl}pyridin-2-yl)-1H-indole-6-carbonitrile hydrochloride**

25

Starting material: 4-(2-{4-[(6-chloropyridin-3-yl)sulfonyl]piperazin-1-yl}ethyl)morpholine. The crude product was purified on a silica gel column using chloroform/methanol/triethylamine, (100:25:1), as the eluent to give the title compound as the base in 40% yield. The base was transformed to the corresponding reddish orange  
30 hydrochloride salt. Yield: 71% of the title compound: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 11.07 (s, 1 H), 8.67 (s, 1 H), 7.89 (m, 2 H), 7.78 (d, *J* = 8.0 Hz, 1 H), 7.44 (d, *J* = 8.0 Hz, 1



H), 7.28 (s, 1 H), 4.07 (br s, 8 H), 3.89 (br s, 4 H), 3.55 (br s, 4 H), 3.27 (br s, 4 H); MS (EI)  $m/z$  497 ( $M^+ + 1$ ).

#### **Example 59**

5 **2-Hydroxy-3-(5-{[4-(2-pyrrolidin-1-ylethyl)piperazin-1-yl]sulfonyl}pyridin-2-yl)-1H-indole-6-carbonitrile hydrochloride**

Starting material: 1-[(6-chloropyridin-3-yl)sulfonyl]-4-(2-pyrrolidin-1-ylethyl)piperazine.

The crude product was purified on a silica gel column using

chloroform/methanol/triethylamine, (100:100:1), as the eluent to give the title compound

10 as the base in 25% yield. The base was transformed to the corresponding reddish orange hydrochloride salt. Yield: 71% of the title compound:  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  11.07 (s, 1 H), 8.67 (s, 1 H), 7.89 (br s, 2 H), 7.78 (d,  $J = 8.0$  Hz, 1 H), 7.44 (dd,  $J = 8.0$ , 1.2 Hz, 1 H), 7.28 (d,  $J = 1.2$  Hz, 1 H), 4.84 (br s, 4 H), 3.58 (br s, 6 H), 3.20 (br s, 6 H), 1.94 (br s, 4 H); MS (EI)  $m/z$  481 ( $M^+ + 1$ ).

15

#### **Example 60**

**2-Hydroxy-3-(5-{[4-(2-methoxyethyl)piperazin-1-yl]sulfonyl}pyridin-2-yl)-1H-indole-6-carbonitrile hydrochloride**

Starting material: 1-[(6-chloropyridin-3-yl)sulfonyl]-4-(2-methoxyethyl)piperazine. The

20 crude product was purified on a silica gel column using

chloroform/methanol/triethylamine, (90:10:1), as the eluent to give the base in 36% yield.

The base was transformed to the hydrochloride salt. Yield: 65% of the title compound:  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  11.07 (s, 1 H), 10.07 (br s, 1 H), 8.67 (s, 1 H), 7.89 (br s, 2 H), 7.79 (d,  $J = 8.0$  Hz, 1 H), 7.44 (d,  $J = 8.0$  Hz, 1 H), 7.29 (s, 1 H), 3.74 (br s, 2 H), 3.68 (br s, 2 H), 3.62 (br s, 1 H), 3.59 (br s, 1 H), 3.36 (br s, 2 H), 3.31 (s, 3 H), 3.24 (br s, 2 H), 3.00 (m, 2 H); MS (EI)  $m/z$  442 ( $M^+ + 1$ ).

25

#### **Example 61**

30 **2-Hydroxy-N-(3-methoxypropyl)-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1H-indole-5-carboxamide hydrochloride**

Starting materials: N-(3-methoxypropyl)-2-oxoindoline-5-carboxamide (0.149 g, 0.6

mmol) and 1-[(6-chloropyridine-3-yl)sulfonyl]-4-methylpiperazine (0.138 g, 0.5 mmol);

described in: Thunus L., *Annales Pharmaceutiques Francaises* 1977, 35, 197-204). The orange base (0.059 g, 0.12 mmol) was treated with HCl in diethyl ether to obtain the orange hydrochloride salt. Yield: 83% of the title compound:  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  10.93 (s, 1 H), 10.84 (br s, 1 H), 8.55 (br s, 1 H), 8.45 (t,  $J = 5.2$  Hz, 1 H), 8.04 (s, 1 H), 7.81 (s, 2 H), 7.63 (d,  $J = 8.4$  Hz, 1 H), 7.00 (d,  $J = 8.0$  Hz, 1 H), 3.80 (d,  $J = 12.8$  Hz, 2 H), 3.53 (d,  $J = 11.6$  Hz, 2 H), 3.43 (m, 2 H), 3.37 (m, 2 H), 3.29 (s, 3 H), 3.19 (m, 2 H), 3.01 (m, 2 H), 2.81 (s, 3 H), 1.82 (m, 2 H); MS (EI)  $m/z$  488 ( $M^+ + 1$ ).

### **Example 62**

#### **2-Hydroxy-*N*-(2-methoxyethyl)-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxamide hydrochloride**

To a suspension of sodium hydride (97%, 0.030 g, 1.25 mmol) in *N,N*-dimethylformamide (1.5 mL) was added *N*-(2-methoxyethyl)-2-oxoindoline-5-carboxamide (0.176 g, 0.75 mmol). The formed mixture was stirred for 5 min at room temperature followed by the addition of 4-[(6-chloro-1-oxidopyridin-3-yl)methyl]morpholine (0.114 g, 0.5 mmol). The resulting reaction mixture was set under an  $\text{N}_2$  atmosphere and stirred for 1 h at 120 °C and then concentrated *in vacuo*. The remaining *N,N*-dimethylformamide was removed by co-evaporation with toluene (1x). The residue was purified on a silica gel column using chloroform/methanol/triethylamine, (90:10:1), as the eluent. The material was dissolved in chloroform (4 mL), and phosphorus trichloride (0.275 g, 2.0 mmol) was added. The reaction mixture was stirred for 1 h at 60 °C and then concentrated *in vacuo*. The residue was purified on a silica gel column using chloroform/methanol/triethylamine, (90:10:1), as the eluent followed by further purification by washing with diethyl ether (3 mL) to give 0.050 g (24% yield) of the title compound as the base. The base (0.050 g, 0.12 mmol) was dissolved in chloroform/methanol, (1:1), and treated with HCl in diethyl ether (1 M) at 0 °C. The resulting yellow crystals were collected by filtration and washed with diethyl ether to obtain 0.029 g (50% yield) of the title compound:  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  11.48 (br s, 1 H), 10.74 (br s, 1 H), 8.54 (br s, 1 H), 8.27 (s, 1 H), 8.11 (d,  $J = 8.0$  Hz, 1 H), 8.03 (s, 1 H), 7.87 (d,  $J = 9.2$  Hz, 1 H), 7.59 (d,  $J = 8.4$  Hz, 1 H), 6.98 (d,  $J = 8.4$  Hz, 1 H), 4.29 (br s, 1 H), 4.00 (d,  $J = 11.2$  Hz, 2 H), 3.87 (d,  $J = 11.2$  Hz, 1 H), 3.83 (d,  $J = 12.4$  Hz, 1 H), 3.50 (br s, 4 H), 3.38 (d,  $J = 12.4$  Hz, 2 H), 3.32 (s, 3 H), 3.13 (m, 2 H); MS (EI)  $m/z$  411 ( $M^+ + 1$ ).

The following Examples, 63-66, were prepared as described for Example 62.

**Example 63**

**2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-N-(pyridin-2-ylmethyl)-1H-indole-5-carboxamide hydrochloride**

Starting material: 2-oxo-N-(pyridin-2-ylmethyl)indoline-5-carboxamide. The hydrochloride salt was obtained as a yellow solid. Yield: 14% of the title compound:  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  11.43 (br s, 1 H), 10.80 (s, 1 H), 9.43 (br s, 1 H), 8.80 (d,  $J$  = 5.2 Hz, 1 H), 8.36 (m, 1 H), 8.27 (s, 1 H), 8.18 (s, 1 H), 8.12 (d,  $J$  = 5.2 Hz, 1 H), 7.97 (d,  $J$  = 9.2 Hz, 1 H), 7.87 (d,  $J$  = 8.0 Hz, 1 H), 7.79 (m, 1 H), 7.64 (d,  $J$  = 9.2 Hz, 1 H), 7.02 (d,  $J$  = 8.0 Hz, 1 H), 4.83 (d,  $J$  = 6.0 Hz, 2 H), 4.29 (br s, 2 H), 4.00 (d,  $J$  = 11.2 Hz, 2 H), 3.86 (d,  $J$  = 12.4 Hz, 1 H), 3.80 (d,  $J$  = 11.2 Hz, 1 H), 3.38 (d,  $J$  = 12.4 Hz, 2 H), 3.11 (m, 2 H); MS (EI)  $m/z$  444 ( $M^+$ +1).

**Example 64**

**2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-N-(2-thienylmethyl)-1H-indole-5-carboxamide hydrochloride**

Starting material: 2-oxo-N-(2-thienylmethyl)indoline-5-carboxamide. The orange yellow free base was treated with HCl in diethyl ether (1 M) to give the title compound. Yield: 87% as a yellow solid:  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  11.12 (br s, 1 H), 10.75 (s, 1 H), 9.11 (t,  $J$  = 6.0 Hz, 1 H), 8.25 (s, 1 H), 8.05 (br s, 2 H), 7.85 (d,  $J$  = 8.8 Hz, 1 H), 7.62 (d,  $J$  = 7.6 Hz, 1 H), 7.42 (d,  $J$  = 5.2 Hz, 1 H), 7.07 (s, 1 H), 7.00 (m, 2 H), 4.72 (d,  $J$  = 5.6 Hz, 2 H), 4.29 (br s, 2 H), 4.00 (d,  $J$  = 11.2 Hz, 2 H), 3.80 (m, 2 H), 3.38 (d,  $J$  = 12.0 Hz, 2 H), 3.14 (m, 2 H); MS (EI)  $m/z$  449 ( $M^+$ +1).

**Example 65**

**2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-N-[2-(2-oxoimidazolidin-1-yl)ethyl]-1H-indole-5-carboxamide hydrochloride**

Starting material: 2-oxo-N-[2-(2-oxoimidazolidin-1-yl)ethyl]indoline-5-carboxamide. The crude product was purified by preparative HPLC (XTerra<sup>®</sup> PrepMS C8 column 10  $\mu\text{m}$ , 30x150 mm; 0.1 M  $\text{NH}_4\text{OAc}$  buffer/acetonitrile, (95:5 to 60:40), as the eluent) to give the title compound as the base in 27% yield. The base was treated with HCl in diethyl ether (1

M) to give the title compound. Yield: 88%: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 11.72 (br s, 1 H), 10.67 (s, 1 H), 8.46 (t, *J* = 5.2 Hz, 1 H), 8.20 (s, 1 H), 8.11 (dd, *J* = 9.2, 1.6 Hz, 1 H), 7.93 (s, 1 H), 7.82 (d, *J* = 9.2 Hz, 1 H), 7.48 (d, *J* = 8.8 Hz, 1 H), 6.91 (d, *J* = 8.4 Hz, 1 H), 4.23 (d, *J* = 4.0 Hz, 2 H), 3.93 (d, *J* = 11.2 Hz, 2 H), 3.80 (t, *J* = 12.0 Hz, 2 H), 3.38 (m, 4 H), 3.32 (d, *J* = 12.0 Hz, 2 H), 3.20 (m, 4 H), 3.03 (m, 2 H); MS (EI) *m/z* 465 (*M*<sup>+</sup>+1).

#### **Example 66**

##### ***N*-[2-(Acetylamino)ethyl]-2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxamide hydrochloride**

Starting material: *N*-[2-(acetylamino)ethyl]-2-oxoindoline-5-carboxamide. Yield: 51%: <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz) δ 7.65 (br s, 1 H), 7.56 (br s, 2 H), 7.37 (m, 1 H), 7.29 (d, *J* = 9.2 Hz, 1 H), 6.97 (d, *J* = 8.4 Hz, 1 H), 3.73 (br s, 4 H), 3.51 (d, *J* = 4.8 Hz, 2 H), 3.46 (d, *J* = 5.6 Hz, 2 H), 3.32 (s, 2 H), 2.52 (br s, 4 H), 2.01 (s, 3 H); MS (EI) *m/z* 438 (*M*<sup>+</sup>+1).

#### **Example 67**

##### **2-Hydroxy-*N*-(2-methoxybenzyl)-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxamide hydrochloride**

A suspension of methyl 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxylate (0.074 g, 0.2 mmol) and 2-methoxybenzylamine (0.069 g, 0.5 mmol) in benzene (2.5 mL) was prepared at room temperature and was set under an N<sub>2</sub> atmosphere. To this mixture, trimethylaluminum (2 M solution in hexane, 0.4 mL, 0.8 mmol) was added via a syringe at 0 °C. After 5 min the reaction mixture was allowed to warm to 70 °C and was kept stirring for 16 h at ambient temperature. The cooled mixture was poured into a saturated sodium hydrogen carbonate solution (10 mL) and extracted with chloroform. The phases were separated, the organic solvent was removed *in vacuo*, and the residue was purified on a silica gel column using chloroform/methanol, (9:1), as the eluent to give 0.075 g (80% yield) of the title compound of the base as a orange yellow solid. The base (0.075 g, 0.16 mmol) was dissolved in chloroform/methanol, (1:1), and treated with HCl in diethyl ether (1 M) at 0 °C followed by addition of diethyl ether. The resulting yellow crystals were collected by filtration and washed with diethyl ether to obtain 0.075 g (86% yield) of the title compound: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) δ 11.27 (br s, 1 H), 10.77 (s, 1 H), 8.88 (t, *J* = 5.6 Hz, 1 H), 8.26 (s, 1 H), 8.11 (s, 1 H), 8.07 (d, *J* = 8.8 Hz, 1 H), 7.88

(d,  $J = 8.8$  Hz, 1 H), 7.64 (d,  $J = 8.0$  Hz, 1 H), 7.28 (t,  $J = 8.0$  Hz, 1 H), 7.23 (d,  $J = 7.2$  Hz, 1 H), 7.05 (d,  $J = 8.4$  Hz, 1 H), 7.00 (d,  $J = 8.4$  Hz, 1 H), 6.94 (t,  $J = 7.2$  Hz, 1 H), 4.54 (d,  $J = 5.6$  Hz, 2 H), 4.28 (br s, 2 H), 4.01 (d,  $J = 11.6$  Hz, 2 H), 3.88 (s, 3 H), 3.81 (m, 2 H), 3.38 (d,  $J = 11.6$  Hz, 2 H), 3.13 (m, 2 H); MS (EI)  $m/z$  473 ( $M^+ + 1$ ).

5

The following Examples, 68-77, were prepared as described for Example 67.

#### Example 68

##### **2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-*N*-[4-(trifluoromethyl)benzyl]-1*H*-indole-5-carboxamide hydrochloride**

10

Starting material: 4-trifluoromethylbenzylamine. Purification on a silica gel column using chloroform/methanol, (9:1), as the eluent, gave the title compound as the base (yellow solid) in 76% yield. The base was treated with HCl in diethyl ether (1 M) to give the title compound. Yield: 88%:  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  11.04 (br s, 1 H), 10.76 (s, 1 H), 9.14 (t,  $J = 5.6$  Hz, 1 H), 8.26 (s, 1 H), 8.10 (s, 1 H), 8.05 (d,  $J = 8.8$  Hz, 1 H), 7.87 (d,  $J = 8.8$  Hz, 1 H), 7.75 (d,  $J = 8.0$  Hz, 2 H), 7.61 (m, 3 H), 7.00 (d,  $J = 8.4$  Hz, 1 H), 4.65 (d,  $J = 5.6$  Hz, 2 H), 4.28 (br s, 2 H), 4.01 (d,  $J = 11.6$  Hz, 2 H), 3.79 (m, 2 H), 3.39 (d,  $J = 11.6$  Hz, 2 H), 3.13 (m, 2 H); MS (EI)  $m/z$  511 ( $M^+ + 1$ ).

15

#### Example 69

##### **2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-*N*-[2-(trifluoromethyl)benzyl]-1*H*-indole-5-carboxamide hydrochloride**

20

Starting material: 2-trifluoromethylbenzylamine. Purification on a silica gel column using chloroform/methanol, (9:1) as the eluent, gave the title compound as the base in 66% yield. The base was treated with HCl in diethyl ether (1 M) to give the title compound. Yield: 82%:  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  11.09 (br s, 1 H), 10.78 (s, 1 H), 9.12 (t,  $J = 5.6$  Hz, 1 H), 8.26 (s, 1 H), 8.14 (s, 1 H), 8.05 (d,  $J = 8.8$  Hz, 1 H), 7.87 (d,  $J = 8.8$  Hz, 1 H), 7.77 (d,  $J = 7.6$  Hz, 1 H), 7.67 (m, 2 H), 7.59 (d,  $J = 8.0$  Hz, 1 H), 7.51 (t,  $J = 7.6$  Hz, 1 H), 7.03 (d,  $J = 8.4$  Hz, 1 H), 4.76 (d,  $J = 5.6$  Hz, 2 H), 4.28 (br s, 2 H), 4.01 (d,  $J = 12.0$  Hz, 2 H), 3.79 (m, 2 H), 3.39 (d,  $J = 12.0$  Hz, 2 H), 3.13 (m, 2 H); MS (EI)  $m/z$  511 ( $M^+ + 1$ ).

25

30

#### Example 70

**2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-N-[2-(trifluoromethoxy)benzyl]-1H-indole-5-carboxamide hydrochloride**

Starting material: 2-trifluoromethoxybenzylamine. The orange-yellow base (0.058 g, 55% yield) was converted to the title compound. Yield: 83%: <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.17 (s, 1 H), 8.13 (s, 1 H), 7.91 (s, 2 H), 7.65 (d, *J* = 8.4 Hz, 1 H), 7.51 (d, *J* = 7.6 Hz, 1 H), 7.37 (m, 3 H), 7.14 (d, *J* = 8.0 Hz, 1 H), 4.72 (s, 2 H), 4.34 (s, 2 H), 4.13 (d, *J* = 12.4 Hz, 2 H), 3.79 (t, *J* = 12.4 Hz, 2 H), 3.51 (m, 2 H), 3.27 (m, 2 H); MS (EI) *m/z* 527 (*M*<sup>+</sup>+1).

**Example 71**

**2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-N-[4-(trifluoromethoxy)benzyl]-1H-indole-5-carboxamide hydrochloride**

Starting material: 4-trifluoromethoxybenzylamine. The orange-yellow base was converted to the title compound. Yield: 96%: <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.20 (s, 1 H), 8.14 (s, 1 H), 7.94 (s, 2 H), 7.65 (d, *J* = 8.4 Hz, 1 H), 7.51 (d, *J* = 7.2 Hz, 2 H), 7.27 (d, *J* = 8.8 Hz, 2 H), 7.14 (d, *J* = 8.0 Hz, 1 H), 4.65 (s, 2 H), 4.34 (s, 2 H), 4.12 (d, *J* = 12.4 Hz, 2 H), 3.79 (t, *J* = 12.4 Hz, 2 H), 3.51 (m, 2 H), 3.27 (m, 2 H); MS (EI) *m/z* 527 (*M*<sup>+</sup>+1).

**Example 72**

**3-{5-[(Diethylamino)methyl]pyridin-2-yl}-2-hydroxy-N-(2-thienylmethyl)-1H-indole-5-carboxamide hydrochloride**

Starting materials: methyl 3-{5-[(diethylamino)methyl]pyridin-2-yl}-2-hydroxy-1H-indole-5-carboxylate (0.071 g, 0.2 mmol) and 2-(aminomethyl)thiophene (0.057 g, 0.5 mmol). The base was obtained as an orange-yellow solid (0.043 g, 50% yield), which was transformed to the orange-yellow hydrochloride salt (0.045 g, 89% yield): <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.20 (s, 1 H), 8.12 (d, *J* = 1.2 Hz, 1 H), 7.94 (s, 2 H), 7.61 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.30 (dd, *J* = 5.2, 1.2 Hz, 1 H), 7.13 (d, *J* = 8.0 Hz, 1 H), 7.07 (m, 1 H), 6.98 (dd, *J* = 5.2, 3.6 Hz, 1 H), 4.79 (s, 2 H), 4.33 (s, 2 H), 3.29 (m, 4 H), 1.41 (t, *J* = 7.2 Hz, 6 H); MS (EI) *m/z* 435 (*M*<sup>+</sup>+1).

**Example 73**

**3-{5-[(Diethylamino)methyl]pyridin-2-yl}-2-hydroxy-N-(pyridin-2-ylmethyl)-1H-indole-5-carboxamide hydrochloride**

Starting materials: methyl 3-{5-[(diethylamino)methyl]pyridin-2-yl}-2-hydroxy-1*H*-indole-5-carboxylate (0.071 g, 0.2 mmol) and 2-(aminomethyl)pyridine (0.054 g, 0.5 mmol). The base was obtained as an orange-yellow solid (0.021 g, 24% yield), which was transformed to the orange-yellow hydrochloride salt (0.015 g, 60% yield): <sup>1</sup>H NMR

(CD<sub>3</sub>OD, 400 MHz) δ 8.81 (d, *J* = 4.8 Hz, 1 H), 8.63 (dt, *J* = 8.0, 1.2 Hz, 1 H), 8.23 (br s, 2 H), 8.15 (d, *J* = 8.0 Hz, 1 H), 8.02 (m, 3 H), 7.70 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.16 (d, *J* = 8.0 Hz, 1 H), 4.97 (s, 2 H), 4.34 (s, 2 H), 3.29 (m, 4 H), 1.41 (t, *J* = 7.2 Hz, 6 H); MS (EI) *m/z* 430 (*M*<sup>+</sup>+1).

#### 10 **Example 74**

##### **3-{5-[(Diethylamino)methyl]pyridin-2-yl}-2-hydroxy-*N*-(2-methoxyethyl)-1*H*-indole-5-carboxamide hydrochloride**

Starting materials: methyl 3-{5-[(diethylamino)methyl]pyridin-2-yl}-2-hydroxy-1*H*-indole-5-carboxylate (0.071 g, 0.2 mmol) and 2-methoxyethylamine (0.037 g, 0.5 mmol).

15 The base was obtained as an orange-yellow solid (0.034 g, 43% yield), which was transformed to the orange-yellow hydrochloride salt (0.033 g, 82% yield): <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.26 (s, 1 H), 8.13 (s, 1 H), 8.00 (s, 2 H), 7.60 (dd, *J* = 8.4, 1.6 Hz, 1 H), 7.16 (d, *J* = 8.0 Hz, 1 H), 4.35 (s, 2 H), 3.41 (s, 3 H), 3.29 (m, 8 H), 1.41 (t, *J* = 7.2 Hz, 6 H); MS (EI) *m/z* 397 (*M*<sup>+</sup>+1).

20

#### **Example 75**

##### **2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-*N*-(tetrahydrofuran-2-ylmethyl)-1*H*-indole-5-carboxamide hydrochloride**

Starting materials: methyl 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxylate and tetrahydrofurfurylamine, but heated at reflux for 2 h. The cooled mixture was poured into a saturated NaHCO<sub>3</sub> solution and concentrated *in vacuo*. The residue was suspended in methanol/dichloromethane, (1:1), silica gel (~2 g) was added and the mixture was re-concentrated *in vacuo*. The resulting residue was purified on a silica gel column using dichloromethane/methanol, (100:1 to 25:2 and 1% ammonia solution in water

25 (25%)), as the eluent to give the base. Yield: 27%: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 300 MHz) δ 14.75 (br s, 1 H), 11.37 (br s, 1 H), 10.69 (s, 1 H), 8.50 (t, *J* = 5.5 Hz, 1 H), 8.22 (s, 1 H), 8.06 (d, *J* = 9.2 Hz, 1 H), 7.99 (s, 1 H), 7.82 (d, *J* = 9.2 Hz, 1 H), 7.54 (d, *J* = 8.1 Hz, 1 H), 6.93 (d,

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$J = 8.1$  Hz, 1 H), 4.25 (s, 2 H), 4.02–3.60 (m, 6 H), 3.44–3.22 (m, 4 H), 3.20–3.03 (m, 2 H), 1.95–1.78 (m, 4 H), 1.70–1.55 (m, 1 H); MS (ES)  $m/z$  437 ( $M^+ + 1$ ). The base was transferred to the hydrochloride.

5 **Example 76**

***N*-Benzyl-2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxamide hydrochloride**

Starting materials: methyl 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxylate and benzylamine. Yield: 52%:  $^1\text{H}$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  14.70 (br s, 1 H), 11.31 (br s, 1 H), 10.71 (s, 1 H), 9.01 (t,  $J = 5.8$  Hz, 1 H), 8.22 (s, 1 H), 8.09–8.00 (m, 2 H), 7.83 (d,  $J = 9.3$  Hz, 1 H), 7.59 (d,  $J = 8.2$  Hz, 1 H), 7.38–7.18 (m, 5 H), 6.95 (d,  $J = 8.2$  Hz, 1 H), 4.53 (d,  $J = 5.8$  Hz, 2 H), 4.25 (s, 2 H), 4.02–3.71 (m, 4 H), 3.37–3.26 (m, 2 H), 3.17–2.99 (m, 2 H); MS (ES)  $m/z$  443 ( $M^+ + 1$ ).

15 **Example 77**

**2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-*N*-propyl-1*H*-indole-5-carboxamide hydrochloride**

Starting material: methyl 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxylate and propylamine, but was purified on a silica gel column using dichloromethane/methanol, (50:1 to 50:5), as the eluent. Yield: 52%:  $^1\text{H}$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  14.71 (br s, 1 H), 11.32 (br s, 1 H), 10.68 (s, 1 H), 8.40 (t,  $J = 5.6$  Hz, 1 H), 8.22 (s, 1 H), 8.05 (d,  $J = 9.3$  Hz, 1 H), 7.97 (s, 1 H), 7.80 (d,  $J = 9.3$  Hz, 1 H), 7.53 (d,  $J = 8.1$  Hz, 1 H), 6.92 (d,  $J = 8.1$  Hz, 1 H), 4.25 (s, 2 H), 4.02–3.83 (m, 2 H), 3.81–3.72 (m, 2 H), 3.39–3.19 (m, 4 H), 3.17–3.02 (m, 2 H), 1.63–1.50 (m, 2 H), 0.91 (t,  $J = 7.4$  Hz, 3 H); MS (ES)  $m/z$  395 ( $M^+ + 1$ ).

**Example 78**

**2-Hydroxy-*N*-(2-methoxyphenyl)-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride**

30 A suspension of methyl 2-hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxylate (0.120 g, 0.28 mmol) and 2-methoxyaniline (0.069 g, 0.56 mmol)



in benzene (15 ml) was prepared at room temperature under an N<sub>2</sub> atmosphere. To this mixture, trimethylaluminium (2 M solution in heptane, 0.7 mL, 1.4 mmol) was added via a syringe. The mixture was stirred for 5 min at room temperature, and was then allowed to warm to 80 °C and stirred at this temperature for 2 h. The cooled mixture was poured into a saturated sodium hydrogen carbonate solution (20 mL), the aqueous layer was separated and extracted with ethyl acetate (containing 5% methanol). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), the solvents were removed *in vacuo*, and the residue was purified on a silica gel column using dichloromethane/methanol/aqueous NH<sub>3</sub>, (70:10:1), as the eluent. Fractions, containing product, were concentrated, the solid residue was suspended in ethyl acetate (3 mL), and filtered to give 0.061 g (42% yield) of the title compound as a base. This material was dissolved in chloroform/methanol, (1:1), and treated with HCl in diethyl ether (1 M) followed by addition of diethyl ether. The resulting yellow crystals were collected by filtration and washed with diethyl ether to afford 0.055 g (80% yield) of the title compound: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 14.61 (br s, 1 H), 10.98 (s, 1 H), 10.80 (br s, 1 H), 9.34 (s, 1 H), 8.53 (s, 1 H), 8.13 (s, 1 H), 7.80-7.71 (m, 3 H), 7.66 (d, *J* = 8.0 Hz, 1 H), 7.18 (t, *J* = 7.5 Hz, 1 H), 7.10 (d, *J* = 8.0 Hz, 1 H), 7.02-6.93 (m, 3 H), 3.84 (s, 3 H), 3.77-3.72 (m, 2 H), 3.51-3.44 (m, 2 H), 3.17-3.11 (m, 2 H), 3.02-2.96 (m, 2 H), 2.76 (s, 3 H); MS (ES) *m/z* 522 (M<sup>+</sup>+1).

The following Examples, 79-85, were prepared as described for Example 78.

#### **Example 79**

##### **2-Hydroxy-*N*-(4-methoxyphenyl)-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride**

Starting materials: methyl 2-hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxylate and 4-methoxyaniline. Yield: 43%: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 14.4 (br s, 1 H), 10.96 (br s, 2 H), 10.06 (s, 1 H), 9.34 (s, 1 H), 8.52 (s, 1 H), 8.12 (s, 1 H), 7.81 (br s, 2 H), 7.73-7.65 (m, 3 H), 7.02 (d, *J* = 8.0 Hz, 1 H), 6.92 (d, *J* = 8.7 Hz, 2 H), 3.77-3.72 (m, 5 H), 3.51-3.43 (m, 2 H), 3.18-3.10 (m, 2 H), 3.04-2.93 (m, 2 H), 2.76 (s, 3 H); MS (ES) *m/z* 522 (M<sup>+</sup>+1).

#### **Example 80**

**2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-N-(pyridin-3-ylmethyl)-1H-indole-5-carboxamide hydrochloride**

Starting materials: methyl 2-hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1H-indole-5-carboxylate and (pyridine-3-ylmethyl)amine, but the reaction mixture was  
5 heated at 70 °C for 1 h. The product was purified on a silica gel column using dichloromethane/methanol/aqueous NH<sub>3</sub>, (100:10:1), as the eluent. Yield: 50%: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 14.4 (br s, 1 H), 11.25 (br s, 1 H), 10.96 (s, 1 H), 9.55 (t, *J* = 5.3 Hz, 1 H), 8.94 (s, 1 H), 8.82 (d, *J* = 5.4 Hz, 1 H), 8.57 (d, *J* = 8.1 Hz, 1 H), 8.52 (s, 1 H), 8.22 (br s, 1 H), 8.07-7.97 (m, 2 H), 7.73 (dd, *J* = 9.5, 1.8 Hz, 1 H), 7.65 (d, *J* = 8.2 Hz, 1  
10 H), 6.98 (d, *J* = 8.2 Hz, 1 H), 4.68 (d, *J* = 5.3 Hz, 2 H), 3.77-3.72 (m, 2 H), 3.49-3.43 (m, 2 H), 3.18-3.12 (m, 2 H), 3.04-2.98 (m, 2 H), 2.75 (s, 3 H); MS (ES) *m/z* 507 (M<sup>+</sup>+1).

**Example 81**

**2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-N-(pyridin-4-ylmethyl)-1H-indole-5-carboxamide hydrochloride**

Starting materials: methyl 2-hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1H-indole-5-carboxylate and (pyridine-4-ylmethyl)amine, but the reaction mixture was  
heated at 75 °C for 9 h. The product was purified on a silica gel column using dichloromethane/methanol/aqueous NH<sub>3</sub>, (60:10:1), as the eluent. Yield: 35%: <sup>1</sup>H NMR  
20 (DMSO-d<sub>6</sub>, 300 MHz) δ 14.5 (br s, 1 H), 11.25 (br s, 1 H), 10.96 (s, 1 H), 9.54 (br s, 1 H), 8.84 (d, *J* = 5.7 Hz, 2 H), 8.53 (s, 1 H), 8.14 (br s, 1 H), 8.00-7.95 (m, 3 H), 7.73 (d, *J* = 9.0 Hz, 1 H), 7.67 (d, *J* = 8.0 Hz, 1 H), 7.01 (d, *J* = 8.0 Hz, 1 H), 4.68 (s, 2 H), 3.76-3.71 (m, 2 H), 3.48-3.43 (m, 2 H), 3.12-2.98 (m, 4 H), 2.75 (s, 3 H); MS (ES) *m/z* 507 (M<sup>+</sup>+1).

**Example 82**

**2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-N-(pyridin-2-ylmethyl)-1H-indole-5-carboxamide hydrochloride**

Starting materials: methyl 2-hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1H-indole-5-carboxylate and (pyridine-2-ylmethyl)amine, but the reaction mixture was  
30 heated at 80 °C for 24 h. After the first 12 h, an additional 5 eqv. of trimethyl aluminium was added to the reaction mixture. Yield: 40%: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 14.57 (br s, 1 H), 11.24 (br s, 1 H), 10.96 (s, 1 H), 9.55 (br s, 1 H), 8.77 (d, *J* = 5.2 Hz, 1 H), 8.50

(s, 1 H), 8.38 (t,  $J = 7.7$  Hz, 1 H), 8.23 (br s, 1 H), 7.99 (d,  $J = 9.3$  Hz, 1 H), 7.90 (d,  $J = 7.7$  Hz, 1 H), 7.82 (dd,  $J = 7.7, 5.2$  Hz, 1 H), 7.70 (d,  $J = 9.3$  Hz, 1 H), 7.64 (d,  $J = 8.0$  Hz, 1 H), 7.01 (d,  $J = 8.0$  Hz, 1 H), 4.68 (d,  $J = 4.5$  Hz, 2 H), 3.76-3.71 (m, 2 H), 3.47-3.43 (m, 2 H), 3.16-2.98 (m, 4 H), 2.73 (s, 3 H); MS (ES)  $m/z$  507 ( $M^+ + 1$ ).

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### **Example 83**

#### ***N*-[2-(Aminosulfonyl)ethyl]-2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxamide hydrochloride**

Starting materials: methyl 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxylate and 2-aminoethanesulfonamide hydrochloride, but the reaction mixture was heated at 80 °C for 22 h. After the first 2 h, an additional 6 eqv. of trimethylaluminium was added to the reaction mixture. The mixture was cooled, diluted with a saturated sodium hydrogen carbonate solution (10 mL) and concentrated *in vacuo*. The residue was suspended in methanol/dichloromethane, (1:1), silica gel (~2 g) was added and the mixture was re-concentrated *in vacuo*, resulting in a fine yellow powder that was purified on a silica gel column using dichloromethane/methanol/aqueous  $NH_3$ , (first 100:10:1, then 70:10:1), as the eluent to afford the title compound as a base in 40% yield:  $^1H$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  14.5 (br s, 1 H), 11.29 (br s, 1 H), 10.69 (s, 1 H), 8.61 (br s, 1 H), 8.22 (s, 1 H), 8.04 (d,  $J = 9.0$  Hz, 1 H), 7.98 (s, 1 H), 7.82 (d,  $J = 9.0$  Hz, 1 H), 7.51 (d,  $J = 8.2$  Hz, 1 H), 6.96-6.90 (m, 3 H), 4.25 (s, 2 H), 3.98-3.64 (m, 14 H), 3.36-3.22 (m, 4 H), 3.12-3.04 (m, 2 H); MS (ES)  $m/z$  460 ( $M^+ + 1$ ). The base was converted to the hydrochloride

15

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### **Example 84**

#### ***2*-Hydroxy-*N*-[2-(methylsulfonyl)ethyl]-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxamide hydrochloride**

Starting materials: methyl 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxylate and 2-aminoethylmethylsulfone hydrochloride, but the reaction mixture was after cooling diluted with a saturated sodium hydrogen carbonate solution (10 mL) and concentrated *in vacuo*. The residue was suspended in methanol/dichloromethane (1:1) and silica gel (~2 g) was added. The mixture was re-concentrated *in vacuo*, resulting in a fine yellow powder that was purified on a silica gel column using

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dichloromethane/methanol/aqueous NH<sub>3</sub>, (100:10:1), as the eluent to afford the title compound as a base in 36% yield: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 14.70 (br s, 1 H), 11.42 (br s, 1 H), 10.71 (s, 1 H), 8.73 (br s, 1 H), 8.22 (s, 1 H), 8.06 (d, *J* = 9.3 Hz, 1 H), 7.99 (s, 1 H), 7.82 (d, *J* = 9.3 Hz, 1 H), 7.52 (d, *J* = 8.2 Hz, 1 H), 6.94 (d, *J* = 8.2 Hz, 1 H), 4.25 (s, 2 H), 3.98-3.92 (m, 2 H), 3.85-3.67 (m, 4 H), 3.44-3.29 (m, 4 H), 3.12-3.00 (m, 5 H); MS (ES) *m/z* 459 (M<sup>+</sup>+1). The base was converted to the hydrochloride.

### Example 85

#### **3-(4-Cyanopyridin-2-yl)-2-hydroxy-*N*-(2-methoxyethyl)-1*H*-indole-5-carboxamide**

Starting material: methyl 3-(4-cyanopyridin-2-yl)-2-hydroxy-1*H*-indole-5-carboxylate and 2-methoxyethanamine. The product was purified on a silica gel column using chloroform/methanol/aqueous NH<sub>3</sub>, (150:10:1), as the eluent. The combined fractions were concentrated, stirred for 2 h in ethyl acetate (5 mL), and the formed precipitate was filtered off to give 0.012 g (8% yield) of the title compound as a dark-red powder: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz) δ 14.67 (br s, 1 H), 10.83 (s, 1 H), 8.46 (br s, 1 H), 8.16 (d, *J* = 6.3 Hz, 1 H), 7.98 (s, 1 H), 7.81 (s, 1 H), 7.56 (d, *J* = 7.8 Hz, 1 H), 6.95 (d, *J* = 7.8 Hz, 1 H), 6.86 (d, *J* = 6.3 Hz, 1 H), 3.48 (br s, 4 H), 3.31 (s, 3 H); MS (ES) *m/z* 337 (M<sup>+</sup>+1).

### Example 86

#### **3-(5-Cyanopyridin-2-yl)-2-hydroxy-*N*-{2-[(4-methylpiperazin-1-yl)sulfonyl]ethyl}-1*H*-indole-5-carboxamide hydrochloride**

Sodium hydride (0.026 g of 60% suspension in mineral oil, 0.65 mmol) was added to a cooled (0 °C) solution of *N*-{2-[(4-methylpiperazin-1-yl)sulfonyl]ethyl}-2-oxoindoline-5-carboxamide (0.120 g, 33 mmol) in *N,N*-dimethylformamide (5 mL). The reaction mixture was stirred at 0 °C for 10 min under an N<sub>2</sub> atmosphere, followed by the addition of 2-chloro-5-cyanopyridine (0.050 g, 0.36 mmol) in *N,N*-dimethylformamide (2 mL). The reaction vessel was closed, immediately warmed up to 100 °C, and the reaction was stirred at this temperature for 1 h. The cooled mixture was diluted with a saturated sodium hydrogen carbonate solution (5 mL) and concentrated *in vacuo*. The residue was suspended in methanol/dichloromethane (1:1), silica gel (~2 g) was added and mixture was re-concentrated *in vacuo*. The solid residue was purified on a silica gel column using dichloromethane/methanol/aqueous NH<sub>3</sub>, (60:10:1), as the eluent. Fractions containing

product were concentrated, the resulting orange foam was suspended in ethyl acetate (3 mL), and filtered to give 0.020 g (13% yield) of the title compound as the base. This material was dissolved in chloroform/methanol, (1:1), and treated with HCl in diethyl ether followed by addition of diethyl ether. The resulting yellow crystals were collected by  
5 filtration and washed with diethyl ether to afford 0.014 g (60% yield) of the title compound:  $^1\text{H}$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  14.68 (br s, 1 H), 10.94 (s, 1 H), 10.55 (br s, 1 H), 8.74 (br s, 1 H), 8.59 (s, 1 H), 8.00 (s, 1 H), 7.86 (d,  $J = 9.0$  Hz, 1 H), 7.70 (d,  $J = 9.0$  Hz, 1 H), 7.60 (d,  $J = 8.1$  Hz, 1 H), 6.98 (d,  $J = 8.1$  Hz, 1 H), 3.83-3.75 (m, 4 H), 3.70-3.62 (m, 2 H), 3.52-3.42 (m, 4 H), 3.27-3.20 (m, 2 H), 3.12-3.05 (m, 2 H), 2.75 (s, 3  
10 H); MS (ES)  $m/z$  469 ( $M^+ + 1$ ).

#### **Example 87**

#### **2-Hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1H-indole-5-carboxamide hydrochloride**

15 Sodium hydride (0.090 g of 60% suspension in mineral oil, 2.25 mmol) was added to a cooled (0 °C) solution of 2-oxoindoline-5-carboxamide (0.315 g, 1.79 mmol) in *N,N*-dimethylformamide (5 mL). The reaction mixture was stirred at 0 °C for 15 min under an  $\text{N}_2$  atmosphere, followed by the addition of 4-[(6-chloro-1-oxidopyridin-3-yl)methyl]morpholine (0.345 g, 1.51 mmol) in *N,N*-dimethylformamide (2 mL). The  
20 reaction vessel was closed, immediately warmed up to 130 °C, and the reaction was stirred at this temperature for 0.5 h. The cooled mixture was diluted with a saturated  $\text{NaHCO}_3$  solution (30 mL), and extracted with ethyl acetate (containing 5% methanol). The combined organic extracts were dried ( $\text{Na}_2\text{SO}_4$ ), and the solvents were removed *in vacuo*. The residue was dissolved in toluene (100 mL), and re-evaporated. The material was dried,  
25 dissolved in ethyl acetate (75 mL), and phosphorus trichloride (0.6 mL, 6 mmol) in ethyl acetate (5 mL) was added dropwise under vigorous stirring. The reaction mixture was heated to reflux for 2 h, cooled to room temperature, and quenched with an excess of saturated sodium hydrogen carbonate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (containing 5% methanol). The combined organic  
30 extracts were dried ( $\text{Na}_2\text{SO}_4$ ), the solvents were removed *in vacuo*, and the residue was purified on a silica gel column using chloroform/methanol/aqueous  $\text{NH}_3$ , (100:10:1), as the eluent to afford the title compound as the base, yield 0.013 g (2.5%). This material was

dissolved in chloroform/methanol (1:1), and treated with HCl in diethyl ether (1 M) followed by addition of diethyl ether. The resulting yellow crystals were collected by filtration and washed with diethyl ether to afford 0.010 g of the title compound:  $^1\text{H}$  NMR (DMSO- $d_6$ , 300 MHz)  $\delta$  14.70 (br s, 1 H), 11.08 (br s, 1 H), 10.68 (s, 1 H), 8.21 (s, 1 H), 8.05-7.95 (m, 2 H), 7.84 (d,  $J = 9.0$  Hz, 1 H), 7.56 (d,  $J = 8.0$  Hz, 1 H), 7.10 (br s, 1 H), 6.92 (d,  $J = 8.0$  Hz, 1 H), 4.26 (s, 2 H), 3.97-3.92 (m, 2 H), 3.80-3.72 (m, 2 H), 3.40-3.33 (m, 2 H), 3.13-3.07 (m, 2 H); MS (ES)  $m/z$  354 ( $M^+ + 1$ ).

### Example 88

#### 10 **2-Hydroxy-3-[5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl]-1H-indole-5-sulfonamide hydrochloride**

To a mixture of sodium hydride (0.024 g, 0.6 mmol, 60% dispersion in oil, pre-washed with hexane) in *N,N*-dimethylformamide (1.5 mL) was added 2-oxoindoline-5-sulfonamide (0.212 g, 1.0 mmol; described in: Sun, Li. et al, *J. Med. Chem.* **1999**, *42*, 5120-5130) in  
15 *N,N*-dimethylformamide (2 mL). The formed mixture was stirred at room temperature for 30 min and 1-[(6-chloropyridin-3-yl)sulfonyl]-4-methylpiperazine (0.92 g, 0.33 mmol; described in: Thunus L. *Annuaire Pharmaceutiques Francisies*, **1977**, *35*, 197-203) in *N,N*-dimethylformamide (2 mL) was added. The obtained solution was heated at 130 °C for 30 min and was then allowed to reach room temperature overnight. The solvent was removed  
20 *in vacuo* and the residue was partitioned between an aqueous sodium hydroxide solution (2 M) and dichloromethane. The combined extracts were evaporated *in vacuo* and co-evaporated with toluene. The residue was purified on a silica gel column using chloroform/methanol/conc.  $\text{NH}_3$  (aq), (80:19:1), as the eluent, to afford 0.010 g. The water phase was evaporated *in vacuo* and purified using the same conditions as above to afford  
25 another 0.014 g. The combined solids were dissolved in warm methanol and treated with HCl in diethyl ether (4 M). The hydrochloride salt was dried at 25 °C *in vacuo* to afford 0.006 g (3% yield) of the title compound: MS (ES)  $m/z$  452 ( $M^+ + 1$ ).

The following Examples, 89-91, were prepared as described for Example 88.

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### Example 89

**2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1H-indole-5-carboxamide hydrochloride**

Starting materials: 2-oxoindoline-5-carboxamide (0.264 g, 1.5 mmol) and sodium hydride (0.048 g, 1.2 mmol, 60% dispersion in oil, pre-washed with hexane) to afford 0.022 g (4% yield) of title compound: <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz) δ 8.07 (s, 1 H), 7.53 (d, *J* = 8 Hz, 1 H), 7.44 (s, 1 H), 7.30 (d, *J* = 8 Hz, 1 H), 7.13 (d, *J* = 10 Hz, 1 H), 6.82 (d, *J* = 8 Hz, 1 H), 3.41-3.25 (m, 4 H), 3.17-3.03 (m, 4 H), 2.67 (br s, 3 H).

**Example 90**

**2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1H-indole-6-carboxamide hydrochloride**

Starting materials: 2-oxoindoline-6-carboxamide (0.264 g, 1.5 mmol) and sodium hydride (0.048 g, 1.2 mmol, 60% dispersion in oil, pre-washed with hexane). Work up: the evaporated residue was purified on a silica gel column using methanol as the eluent.

Fractions containing product were collected, evaporated *in vacuo* and purified on another silica gel column using chloroform/methanol/conc. NH<sub>3</sub> (aq), (72:24:4), as the eluent to afford 0.050 g of the base. The base was dissolved in methanol/acetone and treated with HCl in diethyl ether (4 M). The hydrochloride salt was dried at 55 °C *in vacuo* to afford 0.030 g (6% yield) of the title compound: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ 10.84 (s, 1 H), 10.65 (br s, 1 H), 8.53 (s, 1 H), 7.85 (br s, 1 H), 7.75-7.67 (m, 2 H), 7.60-7.51 (m, 2 H), 7.45 (s, 1 H), 7.11 (br s, 1 H), 3.81-3.64 (m, 2 H), 3.52-3.39 (m, 2 H), 3.19-3.05 (m, 2 H), 3.00-2.85 (m, 2 H), 2.76 (s, 3 H); MS (TSP) *m/z* 416 (M<sup>+</sup>+1).

**Example 91**

**3-[5-({4-[2-(Dimethylamino)ethyl]piperazin-1-yl}sulfonyl)pyridin-2-yl]-2-hydroxy-1H-indole-6-carbonitrile hydrochloride**

Starting materials: 2-oxoindoline-6-carbonitrile (added at 5-10 °C) and (2-{4-[(6-chloropyridin-3-yl)sulfonyl]piperazin-1-yl}ethyl)-*N,N*-dimethylamine. Yield: 8%: <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz) δ 8.19 (s, 1 H), 7.74 (d, *J* = 9 Hz, 1 H), 7.28 (d, *J* = 9 Hz, 1 H), 7.20 (s, 1 H), 7.03 (s, 1 H), 3.43 (t, *J* = 7 Hz, 2 H), 3.34 (m, 4 H), 3.20 (t, *J* = 7 Hz, 2 H), 3.09 (m, 4 H), 2.90 (s, 6 H); MS (ES) *m/z* 455 (M<sup>+</sup>+1).

**Example 92****2-Hydroxy-*N*-(2-methoxyethyl)-3-(5-nitropyridin-2-yl)-1*H*-indole-5-carboxamide hydrochloride**

To a mixture of sodium hydride (0.048 g, 1.2 mmol, 60% dispersion in oil, pre-washed with hexane) in *N,N*-dimethylformamide (2.5 mL) was added *N*-(2-methoxyethyl)-2-oxoindoline-5-carboxamide (0.140 g, 0.6 mmol) in *N,N*-dimethylformamide (1.0 mL) followed by 2-bromo-5-nitropyridine (0.133 g, 0.65 mmol) in *N,N*-dimethylformamide (1.0 mL). The reaction mixture was stirred at room temperature for 15 min and subsequently heated for 2 h at 90 °C. After cooling to room temperature, methanol (5 mL) was added and after 5 min the solvent was removed *in vacuo*. The residue was purified on a silica gel column using chloroform/methanol/conc. NH<sub>3</sub> (aq), (72:24:4), as eluent to afford 0.015 g of the base. The base was dissolved in chloroform/methanol and treated with HCl in diethyl ether (4 M). The hydrochloride salt was dried at 50 °C *in vacuo* over night to afford 6 mg (3% yield) of the title compound: <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ 14.56 (br s, 1 H), 11.00 (s, 1 H), 9.12 (s, 1 H), 8.52-8.46 (m, 1 H), 8.18 (dd, *J* = 10, 2 Hz, 1 H), 8.04 (s, 1 H), 7.68 (d, *J* = 10 Hz, 1 H), 7.64 (dd, *J* = 8, 1 Hz, 1 H), 6.98 (d, *J* = 8 Hz, 1 H), 3.50-3.42 (m, 4 H), 3.28 (s, 3 H); MS (TSP) *m/z* 357 (*M*<sup>+</sup>+1).

**Example 93*****N*-(2-Cyanoethyl)-2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxamide hydrochloride**

To a suspension of sodium hydride (0.043 g, 1.07 mmol, 60% in oil, pre-washed with hexane) in *N,N*-dimethylformamide (2 mL) was added *N*-(2-cyanoethyl)-2-oxoindoline-5-carboxamide (0.150 g, 0.65 mmol) in *N,N*-dimethylformamide (1.0 mL). The mixture was stirred at room temperature for 2 min and 4-[(6-chloro-1-oxidopyridin-3-yl)methyl]morpholine (0.100 g, 0.43 mmol) in *N,N*-dimethylformamide (2.0 mL) was added. The mixture was heated under an atmosphere of nitrogen at 90 °C for 60 min, was then allowed to cool, and the solvent was removed *in vacuo*. The residue was purified on a silica gel column using chloroform/methanol/conc. NH<sub>3</sub> (aq), (84:14:2), as the eluent to afford 0.10 g. The residue was dissolved in chloroform (5 mL) and a concentrated solution of phosphorus trichloride (0.130 g, 0.95 mmol) in chloroform (1 mL) was added. A precipitate was formed, the mixture was heated at 60 °C for 2 h, and was then allowed to



reach room temperature overnight. The solvent was removed *in vacuo* and the residue was purified on a silica gel column using chloroform/methanol/conc.  $\text{NH}_3$  (aq), (88:10:2), as the eluent, to afford 5 mg of the base. The base was dissolved in chloroform and treated with HCl in diethyl ether (4 M). The hydrochloride salt was re-crystallized from acetonitrile, dried at 50 °C *in vacuo* over night to afford 3 mg (1% yield) of the title compound: MS (ES)  $m/z$  406 ( $\text{M}^+ + 1$ ).

#### Example 94

##### 2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1H-indole-5-carbonitrile

A mixture of sodium hydride (0.157 g, 3.9 mmol, 60% dispersion in oil, pre-washed with hexane) in *N,N*-dimethylformamide (2 mL) was added to 2-oxoindoline-5-carbonitrile (0.464 g, 2.9 mmol) in *N,N*-dimethylformamide (5 mL). The formed brown mixture was stirred at room temperature for 10 min and 1-[(6-chloropyridin-3-yl)sulfonyl]-4-methylpiperazine (0.255 g, 0.92 mmol; described in: Thunus L. *Annuale Pharmaceutiques Francisies*, 1977, 35, 197-203) in *N,N*-dimethylformamide (3 mL) was added. The obtained red solution was heated at 150 °C for 10 min and was then allowed to reach room temperature overnight. The solvent was removed *in vacuo* and the residue was partitioned between an aqueous HCl solution (2 M) and ethyl acetate. The aqueous mixture was alkalized to pH 8 by adding sodium hydrogen carbonate (s), and extracted with ethyl acetate (3x10 mL). The combined extracts were dried ( $\text{Na}_2\text{SO}_4$ ), and the solvent was removed *in vacuo*. The residue was purified on a silica gel column using chloroform/methanol/conc.  $\text{NH}_3$  (aq), (84:14:2), as an eluent to afford 0.050 g. Further purification was done by preparative HPLC (Xterra column (19x300 mm) with 0.05 M  $\text{NH}_4\text{OAc}$  buffert/acetonitrile, (90:10-30:70), as a eluent). Fractions containing product were collected, evaporated *in vacuo*, and dried at 25 °C *in vacuo* over night to afford 0.036 g (10% yield) of the title compound:  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 400 MHz)  $\delta$  8.12 (s, 1 H), 7.60 (d,  $J$  = 10 Hz, 1 H), 7.13 (s, 1 H), 7.00 (dd,  $J$  = 8, 2 Hz, 1 H), 6.93 (d,  $J$  = 9 Hz, 1 H), 6.73 (dd,  $J$  = 8, 2 Hz, 1 H), 3.91 (d,  $J$  = 13 Hz, 2 H), 3.60 (d,  $J$  = 11 Hz, 2 H), 3.24 (app. t,  $J$  = 11 Hz, 2 H), 3.02 (app. t,  $J$  = 12 Hz, 2 H), 2.89 (s, 3 H); MS (TSP)  $m/z$  398 ( $\text{M}^+ + 1$ ).

#### Example 95

**2-Hydroxy-*N*-[2-(1*H*-imidazol-4-yl)ethyl]-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride**

To a mixture of 2-hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxylic acid (0.070 g, 0.17 mmol), *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (0.060 g, 0.185 mmol), and 1-hydroxybenzotriazole hydrate (0.025 g, 0.185 mmol) in acetonitrile/*N,N*-dimethylformamide (4 mL, 1:1) was added *N,N*-diisopropylethylamine (0.110 g, 0.84 mmol) in acetonitrile/*N,N*-dimethylformamide (1 mL, 1:1). The reaction was stirred at room temperature for 5 min. 2-(1*H*-Imidazol-4-yl)ethanamine (0.028 g, 0.25 mmol) was added and stirring was continued overnight. The solvents were removed *in vacuo* and the residue was purified on a silica gel column using chloroform/methanol/conc. NH<sub>3</sub> (aq), (80/18/2), as the eluent to afford 0.022 g of the base. The base was dissolved in methanol and treated with HCl in diethyl ether (4 M). The hydrochloride salt was re-crystallized from methanol/ethyl acetate and dried at 55 °C *in vacuo* over night to afford 0.010 g (10% yield) of the title compound: <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz) δ 8.50 (s, 1 H), 8.10 (app. d, *J* = 2 Hz, 1 H), 7.64-7.55 (m, 2 H), 7.35-7.27 (m, 2 H), 7.26 (s, 1 H), 6.95 (d, *J* = 8 Hz, 1 H), 3.68 (t, *J* = 7 Hz, 2 H), 3.47-3.15 (m, 8 H), 3.05 (t, *J* = 7 Hz, 2 H), 2.76 (s, 3 H); MS (ES) *m/z* 510 (M<sup>+</sup>+1).

**Example 96**

***N*-Benzyl-2-hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride**

Sodium hydride (0.033 g of 60% dispersion in paraffin, 0.84 mmol) was washed with hexane, dried *in vacuo* and suspended in *N,N*-dimethylformamide (1 mL). *N*-Benzyl-2-oxoindoline-5-carboxamide (0.110 g, 0.41 mmol) and 1-[(6-chloropyridin-3-yl)sulfonyl]-4-methylpiperazine (0.170 g, 0.62 mmol; described in: Thunus L. *Annuale Pharmaceutiques Francisies*, 1977, 35, 197-203) were dissolved in *N,N*-dimethylformamide (5 mL) and added to the suspension of sodium hydride. The reaction mixture was stirred at room temperature for 10 min and subsequently heated for 1 h at 90 °C. After cooling to room temperature, a saturated aqueous sodium hydrogen carbonate solution was added (4 mL). Silica gel (8 mL) was added and the solvent was removed *in vacuo*. The residue was purified on a silica gel column using a gradient of chloroform/methanol mixtures, (40:1 to 1:1 and 2% triethylamine), as the eluent. The base was dissolved in a mixture of

chloroform (5 mL) and methanol (5 mL). Hydrogen chloride (3 mL, 1 M in diethyl ether) was added and stirring was continued for 10 min. The precipitate was washed with diethyl ether and dried *in vacuo* at 60 °C to give 0.035 g (16% yield) of the title compound: <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz) δ 7.79 (m, 1 H), 7.42 (m, 4 H), 7.37 (m, 1 H), 7.24 (m, 1 H), 7.14 (m, 2 H), 6.80 (m, 1 H), 6.68 (m, 1 H), 4.50 (s, 2 H), 3.77 (m, 2 H), 3.60 (m, 2 H), 3.22 (m, 2 H), 2.91 (m, 5 H); MS (ES) *m/z* 506 (M<sup>+</sup>+1).

The following Examples, 97-100, were prepared as described for Example 96.

**Example 97**

10 **2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-*N*-propyl-1*H*-indole-5-carboxamide hydrochloride**

Starting material: 2-oxo-*N*-propylindoline-5-carboxamide. Yield: 14% of the title compound: <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz) δ 8.06 (d, *J* = 2 Hz, 1 H), 7.49 (dd, *J* = 9, 2 Hz, 1 H), 7.40 (m, 1 H), 7.26 (m, 1 H), 7.11 (m, 1 H), 6.83 (d, *J* = 8 Hz, 1 H), 3.90 (m, 2 H), 3.60 (m, 2 H), 3.29 (t, *J* = 7 Hz, 2 H), 3.24 (m, 2 H), 2.96 (m, 2 H), 2.90 (s, 3 H), 1.62 (sext, *J* = 7 Hz, 2 H), 0.95 (t, *J* = 7 Hz, 3 H); MS (ES) *m/z* 458 (M<sup>+</sup>+1).

**Example 98**

20 **2-Hydroxy-*N*-(2-methoxyethyl)-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride**

Starting material: *N*-(2-methoxyethyl)-2-oxoindoline-5-carboxamide. Yield: 12% of the title compound: <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz) δ 8.06 (d, *J* = 2 Hz, 1 H), 7.51 (dd, *J* = 9, 2 Hz, 1 H), 7.43 (m, 1 H), 7.29 (dd, *J* = 8, 2 Hz, 1 H), 7.14 (d, *J* = 9 Hz, 1 H), 6.84 (d, *J* = 8 Hz, 1 H), 3.92 (m, 2 H), 3.70 (t, *J* = 6 Hz, 2 H), 3.61 (m, 2 H), 3.59 (t, *J* = 5 Hz, 2 H), 3.44 (s, 3 H), 3.26 (m, 2 H), 2.98 (m, 2 H), 2.92 (s, 3 H); MS (ES) *m/z* 474 (M<sup>+</sup>+1).

**Example 99**

***N*-[2-(Dimethylamino)ethyl]-2-hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride**

30 Starting material: *N*-[2-(dimethylamino)ethyl]-2-oxoindoline-5-carboxamide. The residue was purified on a silica gel column using a gradient chloroform/methanol, (40:1 to 1:1 and 3% triethylamine), as the eluent. Yield: 6% of the title compound: <sup>1</sup>H NMR (D<sub>2</sub>O, 400

MHz)  $\delta$  8.28 (m, 1 H), 7.89 (m,  $J = 2$  Hz, 1 H), 7.80 (m, 1 H), 7.61 (m, 1 H), 7.53 (m, 1 H), 7.13 (d,  $J = 8$  Hz, 1 H), 3.94 (m, 2 H), 3.83 (t,  $J = 6$  Hz, 2 H), 3.62 (m, 2 H), 3.45 (t,  $J = 6$  Hz, 2 H), 3.27 (m, 2 H), 3.00 (m, 6 H), 2.96 (m, 2 H), 2.92 (s, 3 H); MS (ES)  $m/z$  487 ( $M^+ + 1$ ).

#### **Example 100**

##### **3-(5-Cyanopyridin-2-yl)-2-hydroxy-*N*-(2-methoxyethyl)-1*H*-indole-5-carboxamide hydrochloride**

Starting materials: *N*-(2-methoxyethyl)-2-oxoindoline-5-carboxamid and 6-

chloronicotinonitrile. The residue was purified on a silica gel column using a gradient chloroform/methanol, (100:1 to 10:1), as the eluent. Yield: 28% of the title compound:  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  10.89 (s, 1 H), 8.56 (m, 1 H), 8.49 (m, 1 H), 7.98 (s, 1 H), 7.85 (dd,  $J = 10$ , 2 Hz, 1 H), 7.70 (d,  $J = 10$  Hz, 1 H), 7.59 (dd,  $J = 9$ , 2 Hz, 1 H) 6.96 (d,  $J = 9$  Hz, 1 H), 3.45 (m, 4 H), 3.27 (s, 3 H); MS (ES)  $m/z$  337 ( $M^+ + 1$ ).

#### **Example 101**

##### **2-Hydroxy-3-[5-(piperidin-1-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxamide hydrochloride**

A solution of 1-[(6-chloro-1-oxidopyridin-3-yl)methyl]piperidine (0.147 g, 0.65 mmol) in dry *N,N*-dimethylformamide (2 mL) was added to a stirred suspension of sodium hydride (0.064 g, 2.6 mmol) in dry *N,N*-dimethylformamide (2 mL) under an atmosphere of nitrogen. After stirring for 5 min at room temperature, 2-oxoindoline-5-carboxamide (0.175 g, 0.99 mmol) was added in one portion. The resulting mixture was stirred at room temperature for another 15 min and then in a pre-heated oil bath at 110 °C for 2 h. The mixture was allowed to return to room temperature and methanol was added. The solvent was evaporated, the residue was dissolved in ethyl acetate, and phosphorous trichloride (0.90 mL) was added. The resulting mixture was heated at 70 °C for 18 h, and was then allowed to return to room temperature. The pH was adjusted to 7 by the addition of aqueous sodium carbonate and the solvent was evaporated. Purification on a silica gel column using dichloromethane/methanol/triethylamine, (8:2:0.1), as the eluent, gave 0.140 g of the base. The base was dissolved in chloroform/methanol, (9:1), and treated with hydrochloric acid (3.6 mL, 1 M in diethyl ether) and the mixture was stirred at room

temperature for 15 min. Diethyl ether was added to give a yellow precipitate that was filtered off and washed with several solvents (chloroform, diethyl ether, ethyl acetate, and methanol) to give 0.026 g (9% yield) of the title compound:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  8.08 (d,  $J = 3$  Hz, 2 H), 7.84 (m, 2 H), 7.59 (m, 1 H), 7.05 (d,  $J = 8$  Hz, 1 H), 4.22 (s, 2 H), 3.54 (m, 2 H), 2.99 (m, 2 H), 1.99 (m, 2 H), 1.81 (m, 3 H), 1.53 (m, 2 H); MS (ES)  $m/z$  351 ( $\text{M}^+ + 1$ ).

#### Example 102

##### **2-Hydroxy-*N*-methyl-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxamide hydrochloride**

The title compound was prepared as described for Example 101 using 4-[(6-chloro-1-oxidopyridin-3-yl)methyl]morpholine and *N*-methyl-2-oxoindoline-5-carboxamide. Yield: 12%;  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 400 MHz)  $\delta$  7.82 (d,  $J = 2$  Hz, 1 H), 7.58 (dd,  $J = 9, 2$  Hz, 1 H), 7.45 (br s, 1 H), 7.28 (m, 2 H), 6.92 (d,  $J = 8$  Hz, 1 H), 4.16 (s, 2 H), 4.12 (m, 2 H), 3.79 (m, 2 H), 3.46 (m, 2 H), 3.24 (m, 2 H), 2.90 (s, 3 H); MS (TSP)  $m/z$  367 ( $\text{M}^+ + 1$ ).

#### Example 103

##### **6-Bromo-2-hydroxy-*N*-methyl-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride**

A solution of 1-[(6-chloropyridine-3-yl)sulfonyl]-4-methylpiperazine (0.048 g, 0.17 mmol; described in: Thunus L. *Annales Pharmaceutiques Francaises* 1977, 35, 197-204) and 6-bromo-*N*-methyl-2-oxoindoline-5-carboxamide (0.47 g, 0.17 mmol) in dry *N,N*-dimethylformamide (2 mL) was added to a stirred suspension of sodium hydride (0.010 g, 0.41 mmol) in dry *N,N*-dimethylformamide (0.5 mL) under an atmosphere of nitrogen. The resulting mixture was stirred at room temperature for 20 min and in a pre-heated oil bath, 110 °C, for 1.5 h. The mixture was allowed to return to room temperature, the solvent was evaporated, and the residue was purified on a silica gel column using dichloromethane/methanol, (9:1), as the eluent to give 0.045 g of the base. The base was dissolved in dichloromethane/methanol, (9:1), and the solution was treated with hydrochloric acid (0.35 mL, 1 M in diethyl ether). The formed precipitate was filtered off, washed with dichloromethane and diethyl ether, and dried *in vacuo* to give 0.021 g (21% yield) of the title compound:  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz)  $\delta$  10.87 (s, 1 H), 10.80 (br s,

1 H), 8.51 (s, 1 H), 8.19 (m, 1 H), 7.70 (m, 2 H), 7.54 (s, 1 H), 7.08 (s, 1 H), 3.73 (m, 2 H), 3.46 (m, 2 H), 3.13 (m, 2 H), 2.95 (m, 2 H), 2.76 (s, 3 H), 2.74 (s, 3 H); MS (ES)  $m/z$  508 and 510 ( $M^+ + 1$ ).

5 The following Examples, 104-109, were prepared as described for Example 103.

#### **Example 104**

##### **6-Bromo-2-hydroxy-*N*-isopropyl-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride**

10 Starting material: 6-bromo-*N*-isopropyl-2-oxoindoline-5-carboxamide. Yield: 34%;  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  10.84 (s, 1 H), 10.50 (br s, 1 H), 8.51 (s, 1 H), 8.10 (d,  $J = 8$  Hz, 1 H), 7.74 (dd,  $J = 10$ , 2 Hz, 1 H), 7.65 (m, 1 H), 7.48 (s, 1 H), 7.07 (s, 1 H), 4.05 (m, 1 H), 3.73 (m, 2 H), 3.47 (m, 2 H), 3.13 (m, 2 H), 2.91 (m, 2 H), 2.77 (s, 3 H), 1.16 (d,  $J = 7$  Hz, 6 H); MS (TSP)  $m/z$  536 and 538 ( $M^+ + 1$ ).

15

#### **Example 105**

##### **6-Bromo-2-hydroxy-*N*-(2-methoxyethyl)-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride**

Starting material: 6-bromo-*N*-(2-methoxyethyl)-2-oxoindoline-5-carboxamide. Yield:  
20 19%;  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  10.87 (s, 1 H), 10.80 (br s, 1 H), 8.51 (s, 1 H), 8.19 (m, 1 H), 7.70 (m, 2 H), 7.54 (s, 1 H), 7.08 (s, 1 H), 3.73 (m, 2 H), 3.46 (m, 2 H), 3.32 (m, 5 H), 2.75 (m, 5 H); MS (ES)  $m/z$  552 and 554 ( $M^+ + 1$ ).

#### **Example 106**

##### **25 6-Bromo-2-hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-*N*-(tetrahydrofuran-2-ylmethyl)-1*H*-indole-5-carboxamide hydrochloride**

Starting material: 6-bromo-2-oxo-*N*-(tetrahydrofuran-2-ylmethyl)indoline-5-carboxamide.  
Yield: 32%;  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 400 MHz)  $\delta$  8.21 (d,  $J = 2$  Hz, 1 H), 7.69 (m, 1 H), 7.13 (s, 1 H), 7.12 (m, 1 H), 6.77 (s, 1 H), 4.26 (m, 1 H), 3.96 (m, 2 H), 3.87 (m, 2 H), 3.63 (m, 3 H),  
30 3.47 (m, 1 H), 3.27 (m, 2 H), 3.06 (m, 2 H), 2.93 (s, 3 H), 2.17 (m, 1 H), 2.02 (m, 2 H), 1.77 (m, 1 H); MS (ES)  $m/z$  578 and 580 ( $M^+ + 1$ ).

**Example 107**

**6-Bromo-2-hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-N-(2-pyrrolidin-1-ylethyl)-1H-indole-5-carboxamide hydrochloride**

Starting material: 6-bromo-2-oxo-N-(2-pyrrolidin-1-ylethyl)indoline-5-carboxamide.

5 Yield: 11%:  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 400 MHz)  $\delta$  8.27 (d,  $J = 2$  Hz, 1 H), 7.78 (m, 1 H), 7.41 (s, 1 H), 7.35 (m, 1 H), 7.09 (s, 1 H), 3.95 (m, 2 H), 3.83 (m, 2 H), 3.75 (m, 2 H), 3.62 (m, 2 H), 3.55 (m, 2 H), 3.24 (m, 4 H), 3.03 (m, 2 H), 2.92 (s, 3 H), 2.20 (m, 2 H), 2.06 (m, 2 H); MS (ES)  $m/z$  591 and 593 ( $\text{M}^+ + 1$ ).

10 **Example 108**

**N-[3-(Dimethylamino)propyl]-2-hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1H-indole-5-carboxamide hydrochloride**

Starting material: N-[3-(dimethylamino)propyl]-2-oxoindoline-5-carboxamide. Yield:

15 32%:  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 400 MHz)  $\delta$  8.07 (d,  $J = 2$  Hz, 1 H), 7.58 (m, 2 H), 7.39 (dd,  $J = 8$ , 2 Hz, 1 H), 7.28 (d,  $J = 10$  Hz, 1 H), 6.96 (d,  $J = 8$  Hz, 1 H), 3.90 (m, 2 H), 3.62 (m, 2 H), 3.49 (m, 2 H), 3.25 (m, 4 H), 2.94 (m, 2 H), 2.92 (s, 6 H), 2.90 (s, 3 H), 2.08 (m, 2 H); MS (ES)  $m/z$  501 ( $\text{M}^+ + 1$ ).

**Example 109**

20 **2-Hydroxy-N-(2-methoxyethyl)-3-[5-(morpholin-4-ylsulfonyl)pyridin-2-yl]-1H-indole-5-carboxamide hydrochloride**

Starting materials: 4-[(6-chloropyridin-3-yl)sulfonyl]morpholine and N-(2-methoxyethyl)-2-oxoindoline-5-carboxamide. Yield: 7%:  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ , 400 MHz)  $\delta$  10.85 (s, 1

25 H), 8.45 (m, 2 H), 7.99 (s, 1 H), 7.74 (s, 2 H), 7.58 (m, 1 H), 6.94 (d,  $J = 8$  Hz, 1 H), 3.65 (m, 4 H), 3.45 (m, 4 H), 3.27 (s, 3 H), 3.00 (m, 4 H); MS (ES)  $m/z$  461 ( $\text{M}^+ + 1$ ).

**Example 110**

**2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-N-pyridin-3-yl-1H-indole-5-carboxamide hydrochloride**

30 Trimethylaluminium (0.505 mL, 1.01 mmol) was added to a suspension of methyl 2-hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1H-indole-5-carboxylate (0.110 g, 0.26 mmol) and 3-aminopyridine (0.024 g, 0.25 mmol) in dry dichloromethane (5

mL), under an atmosphere of nitrogen. The resulting mixture was stirred at room temperature for 10 min and at reflux for 16 h. Water was added, the solid was filtered off, and washed with chloroform. The combined organic phases were evaporated and the residue was purified on a silica gel column using dichloromethane/methanol, (9:1), as the eluent, to give 0.029 g of the base. The base was suspended in dichloromethane/methanol, (9:1), and hydrochloric acid (0.20 mL, 1 M in diethyl ether) was added to give a clear solution and then a yellow precipitate. The solid was filtered off, washed with dichloromethane and diethyl ether, and dried *in vacuo* to give 0.028 g, (19% yield) of the title compound:  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 400 MHz)  $\delta$  9.34 (d,  $J = 3$  Hz, 1 H), 8.61 (m, 1 H), 8.53 (d,  $J = 6$  Hz, 1 H) 8.16 (d,  $J = 2$  Hz, 1 H), 8.01 (dd,  $J = 9, 6$  Hz, 1 H), 7.75 (d,  $J = 1$  Hz, 1 H), 7.67 (dd,  $J = 10, 2$  Hz, 1 H), 7.58 (dd,  $J = 8, 2$  Hz, 1 H), 7.44 (d,  $J = 10$  Hz, 1 H), 7.03 (d,  $J = 8$  Hz, 1 H), 3.87 (m, 2 H), 3.60 (m, 2 H), 3.23 (m, 2 H), 2.94 (m, 2 H), 2.90 (s, 3 H); MS (ES)  $m/z$  493 ( $\text{M}^+ + 1$ ).

### 15 **Example 111**

#### **2-Hydroxy-*N*-(2-methoxybenzylamide)-3-{5-[(4-methylpiperazin-1-yl)sulfon]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride**

To an anhydrous solution of 1-[(6-chloropyridine-3-yl)sulfonyl]-4-methylpiperazine (0.057 g, 0.32 mmol; described in: Thunus L., *Annales Pharmaceutiques Francaises* 1977, 35, 197-204) and sodium hydride (0.019 g, 0.80 mmol) in *N*-methyl pyrrolidinone (1.0 mL) under an atmosphere of nitrogen, was added *N*-(2-methoxybenzyl)-2-oxoindoline-5-carboxamide (0.079 g, 2.67 mmol). The reaction was stirred at room temperature until the gas evolution ceased (20 min), and then heated at 80 °C over night. Aqueous work-up was followed by purification on a silica gel column using methylene chloride/methanol/triethylamine, (90:10:1 to 75:25:1), as the eluent. The substance was further purified by preparative HPLC (Xterra column (19x300 mm) with 0.05 M  $\text{NH}_4\text{OAc}$  buffer/acetonitrile, (90:10-30:70), as the eluent) to give 0.009 g (6% yield) of the yellow title compound as the base:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  6.83 (br s, 1 H), 6.55 (br s, 1 H), 6.25 (m, 2 H), 6.09 (d,  $J = 8$  Hz, 1 H), 5.72 (m, 2 H), 5.53 (d,  $J = 9$  Hz, 1 H), 5.44 (d,  $J = 8$  Hz, 1 H), 5.37 (t,  $J = 8$  Hz, 1 H), 3.07 (s, 2 H), 2.35 (s, 3 H), 1.61 (br s, 4 H), 1.02 (br s, 4 H), 0.76 (s, 3 H); MS (ES)  $m/z$  536 ( $\text{M}^+ + 1$ ),  $m/z$  534 ( $\text{M}^- - 1$ ). The solid was dissolved in a dichloromethane and a small volume of methanol (5 mL total volume). HCl in diethyl



ether (1.0 M) was added until acidic pH. The solvent volume was reduced under vacuum. The precipitated hydrochloride salt was filtered and dried *in vacuo* affording the title compound.

5 The following Examples, 112-114, were prepared as described for Example 111.

#### Example 112

##### **2-Hydroxy-*N*-(3-methoxybenzylamide)-3-{5-[(4-methylpiperazin-1-yl)sulfon]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride**

10 Starting material: *N*-(3-methoxybenzyl)-2-oxoindoline-5-carboxamide. Yield: 7%. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.48 (s, 2 H), 8.32 (s, 1 H), 8.04 (s, 1 H), 7.75-7.68 (m, 2 H), 7.61 (d, *J* = 8 Hz, 1 H), 7.19 (t, *J* = 8 Hz, 1 H), 7.03 (d, *J* = 8 Hz, 1 H), 6.92-6.89 (m, 2 H), 6.78 (d, *J* = 7 Hz, 1 H), 4.54 (s, 2 H), 3.73 (s, 3 H), 3.11 (br s, 4 H), 2.51 (br s, 4 H), 2.26 (s, 3 H); MS (ES) *m/z* 536 (*M*<sup>+</sup>+1), *m/z* 534 (*M*<sup>-</sup>-1). The substance was subsequently  
15 converted into the hydrochloride.

#### Example 113

##### **2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfon]pyridin-2-yl}-*N*-(tetrahydro-2*H*-pyran-4-yl)-1*H*-indole-5-carboxamide hydrochloride**

20 Starting material: 2-oxo-*N*-(tetrahydro-2*H*-pyran-4-yl)indoline-5-carboxamide. Yield: 17%. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ 10.85 (s, 1 H), 8.45 (s, 1 H), 8.14 (br s, 1 H), 7.94 (br s, 1 H), 7.77 (br s, 1 H), 7.69 (br s, 1 H), 7.57 (br s, 1 H), 6.92 (br s, 1 H), 3.90 (d, *J* = 11 Hz, 2 H), 3.39 (t, *J* = 11 Hz, 2 H), 3.00 (br s, 4 H), 2.38 (br s, 4 H), 2.32 (m, 1 H), 2.06 (s, 3 H), 1.76 (d, *J* = 11 Hz, 2 H), 1.62 (m, 2 H); MS (ES) *m/z* 500 (*M*<sup>+</sup>+1), *m/z* 498 (*M*<sup>-</sup>-1).  
25 The substance was subsequently converted into the hydrochloride.

#### Example 114

##### **2-Hydroxy-*N*-(4-methoxybenzylamide)-3-{5-[(4-methylpiperazin-1-yl)sulfon]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride**

30 Starting materials: *N*-(4-methoxybenzyl)-2-oxoindoline-5-carboxamide and 4-[(6-chloro-1-oxidopyridin-3-yl)methyl]morpholine. The product was purified on a silica gel column using dichloromethane/methanol/triethylamine, (90:10:1), as the eluent. The product

fractions were dried under vacuum and taken up in dry dichloromethane, to which was added phosphorus trichloride (0.104 mL, 1.20 mmol). After stirring at 60 °C for 1 h, the reaction was extracted under basic conditions and purified by preparative HPLC (Xterra column (19x300 mm) with 0.05 M NH<sub>4</sub>OAc buffer/acetonitrile, (90:10-30:70), as the eluent). Total yield: 7%: <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.03 (s, 1 H), 7.90 (s, 1 H), 7.82 (s, 2 H), 7.54 (d, *J* = 9 Hz, 1 H), 7.30 (d, *J* = 8 Hz, 2 H), 7.05 (d, *J* = 9 Hz, 1 H), 6.88 (d, *J* = 10 Hz, 2 H), 4.53 (d, 2 H), 3.75 (s, 3 H), 3.69 (br s, 4 H), 3.41 (s, 2 H), 2.47 (br s, 4 H); MS (ES) *m/z* 473 (*M*<sup>+</sup>+1), *m/z* 471 (*M*<sup>-</sup>-1). The substance was subsequently converted into the hydrochloride.

#### **Example 115**

##### ***N*-(Cyanomethyl)-2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxamide hydrochloride**

To a solution of methyl 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxylate (0.090 g, 0.245 mmol), trimethylaluminum (0.98 mL, 1.96 mmol), and triethylamine (0.10 mL, 0.74 mmol) in benzene (4.0 mL) under nitrogen atmosphere, was added aminoacetonitrile hydrochloride (0.056 g, 0.61 mmol). The reaction mixture was stirred at 60 °C overnight. The reaction was extracted with dichloromethane and brine, dried over sodium sulfate and evaporated to dryness. The residue was subsequently purified by preparative HPLC (Xterra C<sub>18</sub> column (19x300 mm) with 0.05 M NH<sub>4</sub>OAc buffer/acetonitrile) to give 8.6 mg (9% yield) of the yellow base: MS (ES) *m/z* 392 (*M*<sup>+</sup>+1). The base was dissolved in a dichloromethane and a small volume of methanol (5 mL total volume.) and HCl in diethyl ether (1.0 M) was added until acidic pH. The solvent volume was reduced under vacuum. The precipitated hydrochloride salt was filtered and dried *in vacuo* affording the title compound.

#### **Example 116**

##### ***N*-(2-Furylmethyl)-2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxamide hydrochloride**

The title compound was prepared as described for Example 115 using methyl 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxylate. Yield: 44%: <sup>1</sup>H NMR

(CD<sub>3</sub>OD, 400 MHz)  $\delta$  7.98 (s, 1 H), 7.88 (s, 1 H), 7.81 (s, 2 H), 7.49 (d,  $J$  = 8 Hz, 1 H), 7.38 (s, 1 H), 6.99 (d,  $J$  = 8 Hz, 1 H) 6.28 (d,  $J$  = 21 Hz, 2 H), 4.54 (s, 2 H), 3.56 (br s, 4 H), 3.39 (s, 2 H), 2.44 (br s, 4 H); MS (ES)  $m/z$  433 ( $M^+$ +1). The substance was subsequently converted into the hydrochloride.

5

**Example 117****2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)methyl]pyridin-2-yl}-1H-indole-6-carbonitrile hydrochloride**

To a suspension of 1-[(6-chloro-1-oxidopyridin-3-yl)methyl]-4-methylpiperazine (0.145 g, 10 0.60 mmol) and 2-oxoindoline-6-carbonitrile (0.100 g, 0.63 mmol) in tetrahydrofuran (3 mL), was added sodium bis(trimethylsilyl)amide (1.4 mL, 1.4 mmol). The mixture was stirred for 5 min at room temperature and then heated in a microwave oven at 110 °C for 10 min. The mixture was quenched with methanol (2 mL) followed by evaporation to dryness. The dry product mixture was dissolved in ethyl acetate/acetonitrile, (1:1, 5 mL), and phosphorus trichloride (0.5 mL, 5.73 mmol) was added. The mixture was stirred at 15 °C for 3 h and then concentrated *in vacuo*. The residue was purified on a silica gel column using a gradient dichloromethane/methanol, (100:1 to 2:1), as the eluent. The resulting yellow solid was dissolved in dichloromethane/methanol, (9:1), and treated with HCl in diethyl ether (1 M) at 0 °C. The resulting yellow crystals were collected by filtration and 20 washed with diethyl ether to obtain 0.025 g (9% yield) of the title compound: MS (ESP)  $m/z$  348 ( $M^+$ +1).

**Example 118****2-Hydroxy-3-[5-(piperidin-1-ylmethyl)pyridin-2-yl]-1H-indole-6-carbonitrile hydrochloride**

25

The title compound was prepared as described for Example 117. Starting material: 1-[(6-chloro-1-oxidopyridin-3-yl)methyl]piperidine (0.136 g, 0.60 mmol) and 2-oxoindoline-6-carbonitrile (0.100 g, 0.63 mmol) and sodium bis(trimethylsilyl)amide (1.4 mL, 1.4 mmol). Yield: 0.031 g, 12%: <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz)  $\delta$  8.01 (d,  $J$  = 2 Hz, 1 H), 7.75 (dd,  $J$  = 9, 2 30 Hz, 1 H), 7.28 (d,  $J$  = 9 Hz, 1 H), 7.06 (m, 2 H), 6.92 (s, 1 H), 4.19 (s, 2 H), 3.53 (m, 2 H), 2.98 (m, 2 H), 1.94 (s, 2 H), 1.82 (m, 1 H), 1.70 (m, 2 H), 1.46 (m, 1 H); MS (ESP)  $m/z$  349 ( $M^+$ +1).

**Example 119****2-Hydroxy-3-{5-[(3-oxopiperazin-1-yl)methyl]pyridin-2-yl}-1H-indole-6-carbonitrile hydrochloride**

5 2-Oxoindoline-6-carbonitrile (0.063 g, 0.397 mmol) was added to a suspension of 4-[(6-chloro-1-oxidopyridin-3-yl)methyl]piperazin-2-one (0.080 g, 0.33 mmol) and sodium hydride (0.042 g, 1.75 mmol) in 1-methyl-2-pyrrolidone (3 mL). The mixture was stirred at room temperature for 10 min, heated at 90 °C for 1 h and finally quenched with methanol (0.5 mL). Trituration with acetonitrile and drying *in vacuo* gave the crude 2-hydroxy-3-{1-  
10 oxido-5-[(3-oxopiperazin-1-yl)methyl]pyridin-2-yl}-1H-indole-6-carbonitrile as a solid. The crude intermediate was suspended in chloroform (5 mL) and phosphorus trichloride (0.5 mL, 5.73 mmol) was added. The mixture was stirred at 60 °C for 3 h and then concentrated *in vacuo*. Purification using preparative HPLC (XTerra®PrepMS C8 column 10 µm, 30x150 mm; 0.1 M NH<sub>4</sub>OAc buffer/acetonitrile, (80:20-20:80), as the eluent) gave  
15 a yellow solid that was dissolved in dichloromethane/methanol, (9:1), and treated with HCl in diethyl ether (1 M) at 0 °C. The resulting yellow crystals were collected by filtration, washed with diethyl ether, and dried to obtain 0.036 g (26% yield) of the title compound: <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz) δ 8.16 (d, *J* = 2 Hz, 1 H), 7.96 (dd, *J* = 9, 2 Hz, 1 H), 7.80 (d, *J* = 9 Hz, 1 H), 7.61 (d, *J* = 8 Hz, 1 H), 7.35 (dd, *J* = 8, 1 Hz, 1 H), 7.31 (s, 1 H), 4.11 (s, 2  
20 H), 3.62 (s, 2 H), 3.51 (t, *J* = 5 Hz, 2 H); MS (ESP) *m/z* 348 (M<sup>+</sup>+1).

**Example 120****2-Hydroxy-3-[6-(2-morpholin-4-ylethoxy)pyrimidin-4-yl]-1H-indole-6-carbonitrile hydrochloride**

25 A mixture of 4-{2-[(6-chloropyrimidin-4-yl)oxy]ethyl}morpholine (0.116 g, 0.47 mmol), 2-oxoindoline-6-carbonitrile (0.075 g, 0.47 mmol) and cesium carbonate (0.46 g, 1.42 mmol) in butyronitrile (3 mL), was heated in a microwave oven at 160 °C for 10 min. The crude product was purified using preparative HPLC (XTerra®PrepMS C8 column 10 µm, 30x150 mm; 0.1 M NH<sub>4</sub>OAc buffer/acetonitrile, (80:20-20:80), as the eluent). The  
30 acetonitrile was evaporated and the remaining aqueous phase was extracted with chloroform and evaporated *in vacuo* to give a yellow solid. The solid was dissolved in dichloromethane/methanol, (9:1), and treated with HCl in diethyl ether (1 M) at 0 °C. The

resulting yellow crystals were collected by filtration, washed with diethyl ether, and dried to obtain 0.036 g (17% yield) of the title compound:  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 400 MHz)  $\delta$  8.31 (s, 1 H), 7.15 (dd,  $J = 8$ , 2 Hz, 1 H), 6.96 (d,  $J = 8$  Hz, 1 H), 6.93 (d,  $J = 2$  Hz, 1 H), 6.01 (s, 1 H), 4.67 (m, 2 H), 4.17 (m, 2 H), 3.94 (m, 2 H), 3.75 (m, 2 H), 3.66 (m, 2 H), 3.40 (m, 2 H); MS (ESP)  $m/z$  366 ( $\text{M}^+ + 1$ ).

#### **Example 121**

##### **3-{6-[2-(Diisopropylamino)ethoxy]pyrimidin-4-yl}-2-hydroxy-1H-indole-6-carbonitrile hydrochloride**

The title compound was prepared as described for Example 120 using *N*-{2-[(6-chloropyrimidin-4-yl)oxy]ethyl}-*N*-isopropylpropan-2-amine (0.10 g, 0.39 mmol), 2-oxoindoline-6-carbonitrile (0.074 g, 0.47 mmol) and cesium carbonate (0.50 g, 1.54 mmol). Yield 0.026 g, 15%:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  8.59 (s, 1 H), 7.81 (d,  $J = 8$  Hz, 1 H), 7.55 (d,  $J = 1$  Hz, 1 H), 7.45 (dd,  $J = 8$ , 1 Hz, 1 H), 6.64 (s, 1 H), 4.40 (t,  $J = 6$  Hz, 1 H), 3.87 (m, 1 H), 3.58 (t,  $J = 6$  Hz, 1 H), 1.44 (m, 3 H); MS (ESP)  $m/z$  380 ( $\text{M}^+ + 1$ ).

#### **Example 122**

##### **2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1H-indole-5-carboxylic acid hydrochloride**

To a mixture of 2-hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1H-indole-5-carbonitrile (0.100 g, 0.25 mmol) in water (2 mL) was added 1 M aqueous sodium hydroxide solution (1.3 mL, 1.3 mmol) followed by water (1 mL) in a microwave vial. The mixture was subjected to microwave irradiation for 15 min at 140 °C. The pH was adjusted to 5 with HCl (aq) (2 M). The solid was collected by filtration, washed with diethyl ether, and dried to afford 0.110 g (89% yield) of the title compound: MS (ESP)  $m/z$  417 ( $\text{M}^+ + 1$ ).

#### **Example 123**

##### **2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-*N*-[3-(2-oxopyrrolidin-1-yl)propyl]-1H-indole-5-carboxamide hydrochloride**

2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1H-indole-5-carboxylic acid (0.050 g, 0.12 mmol), *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium

tetrafluoroborate (0.042 g, 0.13 mmol), 1-hydroxybenzotriazole hydrate (0.018 g, 0.13 mmol) and *N,N*-diisopropylethylamine (0.150 mL, 0.86 mmol) were suspended in *N,N*-dimethylformamide (3 mL), and stirred at room temperature for 30 min. 1-(3-Aminopropyl)pyrrolidin-2-one (0.034 g, 0.24 mmol) was added and stirring was continued  
5 for 1 h. The solvent was removed *in vacuo* and the residue was purified using preparative HPLC (XTerra® PrepMS C8 column 10 µm, 30x150 mm; 0.1 M NH<sub>4</sub>OAc buffer/acetonitrile, (80:20-20:80), as the eluent) to give a yellow/red solid that was dissolved in dichloromethane/methanol (1:1), and treated with HCl in diethyl ether (1 M) at 0 °C. The resulting yellow crystals were collected by filtration and washed with diethyl  
10 ether to obtain 9 mg (12% yield) of the title compound: <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz) δ 1.89 (dd, *J* = 14.0, 7.2 Hz, 2 H) 2.04 (m, 2 H) 2.42 (t, *J* = 8.2 Hz, 2 H) 2.91 (d, *J* = 4.8 Hz, 3 H) 2.99 (m, 2 H) 3.25 (m, 2 H) 3.37 (m, 4 H) 3.53 (t, *J* = 7.2 Hz, 2 H) 3.65 (d, 2 H) 3.91 (d, 2 H) 6.96 (d, *J* = 8.3 Hz, 1 H) 7.35 (m, 2 H) 7.62 (m, 2 H) 8.15 (d, *J* = 2.0 Hz, 1 H); MS (ESP) *m/z* 541 (M<sup>+</sup>+1).

15

The following Examples, 124-133, were prepared as described for Example 123.

#### Example 124

**2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-*N*-(2-thienylmethyl)-  
20 *1H*-indole-5-carboxamide hydrochloride**

Starting material: (2-thienylmethyl)amine. Yield: 16% as a solid: <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz) δ 8.15 (d, *J* = 2 Hz, 1 H), 7.67 (m, 1 H), 7.51 (dd, *J* = 10, 2 Hz, 1 H), 7.33 (d, *J* = 8 Hz, 1 H), 7.30 (dd, *J* = 5, 1 Hz, 1 H), 7.05 (d, *J* = 3 Hz, 1 H), 6.97 (m, 1 H), 6.90 (d, *J* = 8 Hz, 1 H), 3.86 (m, 2 H), 3.55 (m, 2 H), 3.20 (m, 2 H), 2.93 (m, 2 H), 2.87 (s, 3 H); MS  
25 (ESP) *m/z* 512 (M<sup>+</sup>+1).

#### Example 125

**2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-*N*-[2-(2-oxoimidazolidin-1-yl)ethyl]-*1H*-indole-5-carboxamide hydrochloride**

30 Starting material: 1-(2-aminoethyl)imidazolidin-2-one. Yield: 11% as a solid

<sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz) δ 8.11 (d, *J* = 2 Hz, 1 H), 7.61 (dd, *J* = 9, 2 Hz, 1 H), 7.56 (s, 1 H), 7.34 (m, 2 H), 6.95 (d, *J* = 8 Hz, 1 H), 3.90 (m, 2 H), 3.60 (m, 6 H), 3.42 (m, 4 H), 3.26 (m, 2 H), 2.94 (m, 2 H), 2.91 (s, 3 H); MS (ESP) *m/z* 528 (M<sup>+</sup>+1).

5    **Example 126**

**2-Hydroxy-3-[5-(4-methylpiperazine-1-sulfonyl)pyridin-2-yl]-1H-indole-5-carboxylic acid (2-carbamoylethyl)amide**

Starting material: δ-alaninamide. Yield: 12 % as a solid: <sup>1</sup>H NMR (D<sub>2</sub>O, 400 MHz) δ 8.03 (d, *J* = 2 Hz, 1 H), 7.48 (dd, *J* = 9, 2 Hz, 1 H), 7.33 (s, 1 H), 7.23 (d, *J* = 8 Hz, 1 H), 7.05 (d, *J* = 10 Hz, 1 H), 6.79 (d, *J* = 8 Hz, 1 H), 3.91 (d, *J* = 13 Hz, 2 H), 3.63 (m, 4 H), 3.26 (m, 2 H), 2.99 (m, 2 H), 2.92 (s, 3 H), 2.63 (t, *J* = 7 Hz, 2 H); MS (ESP) *m/z* 487 (M<sup>+</sup>+1).

**Example 127**

15    **2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-N-[2-(2-thienyl)ethyl]-1H-indole-5-carboxamide hydrochloride**

Starting material: [2-(2-thienyl)ethyl]amine. Yield: 18% as a solid: <sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.41 (d, *J* = 2 Hz, 1 H), 8.01 (s, 1 H), 7.79 (m, 2 H), 7.56 (dd, *J* = 8, 1 Hz, 1 H), 7.21 (d, *J* = 4 Hz, 1 H), 7.05 (d, *J* = 8 Hz, 1 H), 6.93 (m, 2 H), 3.97 (d, *J* = 14 Hz, 2 H), 3.65 (m, 4 H), 3.23 (m, 2 H), 3.17 (t, *J* = 7 Hz, 2 H), 2.97 (m, 2 H), 2.94 (s, 3 H); MS (ESP) *m/z* 526 (M<sup>+</sup>+1).

**Example 128**

**N-[2-(Acetylamino)ethyl]-2-hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1H-indole-5-carboxamide hydrochloride**

25    Starting material: N-(2-aminoethyl)acetamide. Yield: 22% as a solid  
<sup>1</sup>H NMR (CD<sub>3</sub>OD, 400 MHz) δ 8.41 (s, 1 H), 8.03 (d, *J* = 2 Hz, 1 H), 7.81 (d, *J* = 2 Hz, 2 H), 7.58 (dd, *J* = 8, 2 Hz, 1 H), 7.06 (d, *J* = 8 Hz, 1 H), 3.97 (d, *J* = 13 Hz, 2 H), 3.62 (d, *J* = 13 Hz, 2 H), 3.52 (t, *J* = 6 Hz, 2 H), 3.44 (t, *J* = 6 Hz, 2 H), 3.24 (m, 2 H), 2.99 (m, 2 H), 2.93 (m, 3 H), 1.95 (m, 3 H); MS (ESP) *m/z* 501 (M<sup>+</sup>+1).

30    **Example 129**

***N*-(2-Cyanoethyl)-2-hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride**

Starting material: 3-aminopropanenitrile. Yield: 11% as a solid:  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 400 MHz)  $\delta$  8.07 (d,  $J = 2$  Hz, 1 H), 7.54 (d,  $J = 2$  Hz, 1 H), 7.48 (s, 1 H), 7.34 (d,  $J = 8$  Hz, 1 H), 7.14 (d,  $J = 9$  Hz, 1 H), 6.89 (d,  $J = 8$  Hz, 1 H), 3.92 (m, 2 H), 3.69 (t,  $J = 6$  Hz, 2 H), 3.62 (m, 2 H), 3.26 (m, 2 H), 2.98 (m, 2H), 2.91 (s, 3H), 2.89 (m, 2 H); MS (ESP)  $m/z$  469 ( $\text{M}^+ + 1$ ).

**Example 130**

***N*-[2-(Aminosulfonyl)ethyl]-2-hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride**

Starting material: 2-aminoethanesulfonamide. Yield: 24% as a solid:  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  10.91 (s, 1 H), 10.71 (s, 1 H), 8.63 (s, 1 H), 8.51 (s, 1 H), 8.01 (s, 1 H), 7.76 (s, 2 H), 7.57 (dd,  $J = 8$ , 1 Hz, 1 H), 6.96 (m, 3 H), 3.97 (m, 4 H), 3.74 (d,  $J = 12$  Hz, 2 H), 3.66 (m, 2 H), 3.47 (s, 3 H), 3.25 (m, 2 H), 3.14 (m, 2 H), 2.95 (m, 2 H), 2.77 (d,  $J = 3$  Hz, 3 H); MS (ESP)  $m/z$  523 ( $\text{M}^+ + 1$ ).

**Example 131**

***N*-(Cyanomethyl)-2-hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-1*H*-indole-5-carboxamide hydrochloride**

Starting material: aminoacetonitrile. Yield: 17% as a solid:  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz)  $\delta$  11.04 (m, 1 H), 10.93 (s, 1 H), 8.95 (t,  $J = 6$  Hz, 1 H), 8.51 (s, 1 H), 8.07 (s, 1 H), 7.75 (m, 2 H), 7.61 (m, 1 H), 6.98 (m, 1 H), 4.02 (d,  $J = 6$  Hz, 2 H), 3.74 (d,  $J = 12$  Hz, 2 H), 3.65 (s, 2 H), 3.46 (d,  $J = 12$  Hz, 2 H), 3.12 (m, 2 H), 3.00 (m, 2 H), 2.75 (d,  $J = 4$  Hz, 3 H); MS (ESP)  $m/z$  455 ( $\text{M}^+ + 1$ ).

**Example 132**

**2-Hydroxy-3-[5-(4-methylpiperazine-1-sulfonyl)pyridin-2-yl]-1*H*-indole-5-carboxylic acid carbamoylmethylamide hydrochloride**

Starting material: glycineamide. Yield: 24% as a solid:  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz)  $\delta$  10.91 (s, 1 H), 10.71 (m, 1 H), 8.64 (t,  $J = 6$  Hz, 1 H), 8.50 (s, 1 H), 8.06 (s, 1 H), 7.76 (m, 2 H), 7.61 (dd,  $J = 8$ , 2 Hz, 1 H), 7.35 (s, 1 H), 6.98 (m, 2 H), 3.83 (d,  $J = 6$  Hz, 2 H), 3.74



(d,  $J = 12$  Hz, 2 H), 3.46 (m, 2 H), 3.15 (m, 2 H), 2.96 (m, 2 H), 2.76 (d,  $J = 3$  Hz, 3 H):  
MS (ESP)  $m/z$  473 ( $M^+ + 1$ ).

### Example 133

5    **2-Hydroxy-3-{5-[(4-methylpiperazin-1-yl)sulfonyl]pyridin-2-yl}-*N*-[2-(methylsulfonyl)ethyl]-1*H*-indole-5-carboxamide hydrochloride**

Starting material: [2-(methylsulfonyl)ethyl]amine. Yield: 11% as a solid:  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  10.92 (s, 1 H), 9.99 (m, 1 H), 8.64 (s, 1 H), 8.51 (s, 1 H), 7.99 (s, 1 H), 7.78 (m, 1 H), 7.71 (d,  $J = 9$  Hz, 1 H), 7.57 (dd,  $J = 8, 1$  Hz, 1 H), 6.97 (d,  $J = 8$  Hz, 1 H), 3.50 (m, 2 H), 3.76 (m, 2 H), 3.39 (t,  $J = 7$  Hz, 1 H), 3.33 (s, 3 H), 3.04 (s, 2 H), 2.88 (m, 2 H), 2.79 (s, 2 H); MS (ESP)  $m/z$  522 ( $M^+ + 1$ ).

### Example 134

15    **Methyl 3-fluoro-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-2-oxoindoline-5-carboxylate hydrochloride**

Methyl 2-hydroxy-3-[5-(morpholin-4-ylmethyl)pyridin-2-yl]-1*H*-indole-5-carboxylate (0.074 g, 0.2 mmol) was dissolved in a tetrahydrofuran/dioxane (10 mL, 1:1) mixture under  $\text{N}_2$  atmosphere and stirred at  $-20^\circ\text{C}$  for 5 min. To this solution, sodium bis(trimethylsilyl)amide (1 M solution in tetrahydrofuran, 0.20 mL, 0.2 mmol) was added via a syringe and the reaction mixture was allowed to stir for 20 min at  $0^\circ\text{C}$ . To this mixture 1-fluoro-2,4,6-trimethylpyridinium triflate was added as a solid and the reaction was allowed to warm up to room temperature and stirred for 16 h. The solvent was removed *in vacuo* and the residue was purified on a silica gel column using chloroform/methanol, (9:1), as the eluent. The product was further purified by preparative HPLC (XTerra<sup>®</sup> PrepMS C8 column 10  $\mu\text{m}$ , 19x300 mm; 0.1 M  $\text{NH}_4\text{OAc}$  buffer/acetonitrile, (from 9:1 to 1:1), as eluent gradient) affording 0.020 g (26% yield) of the base as an orange-yellow oil. The base (0.020 g, 0.05 mmol) was dissolved in chloroform/methanol, (1:1), and treated with 1 M hydrochloric acid in diethyl ether at  $0^\circ\text{C}$ . The resulting yellow crystals were collected by vacuum filtration and washed with diethyl ether to obtain 0.016 g (70% yield) of the title compound.  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz)  $\delta$  11.47 (s, 1 H), 8.70 (s, 1 H), 8.33 (d,  $J = 8.0$  Hz, 1 H), 8.07 (d,  $J = 8.4$  Hz, 1 H), 8.03 (d,  $J = 7.6$  Hz, 1 H), 7.56 (s, 1 H), 7.17 (d,  $J = 8.0$  Hz, 1 H), 4.43 (s, 2 H), 3.98 (d,  $J =$

12.4 Hz, 2 H), 3.82 (s, 3 H), 3.76 (m, 2 H), 3.30 (d,  $J = 12.4$  Hz, 2 H), 3.15 (m, 2 H); MS (EI)  $m/z$  386 ( $M^+ + 1$ ).

5    **Example 135**

**2-Hydroxy-3-[5-(4-methyl-piperazin-1-ylmethyl)-pyridin-2-yl]-1H-indole-5-carboxylic acid methyl ester**

The title compound was prepared as described for Example 46 using 1-[(6-chloro-1-oxidopyridin-3-yl)methyl]-4-methylpiperazine (0.967 g, 4.0 mmol) as the starting material.

10    The product was obtained as an orange yellow solid (0.140 g, 9% yield):  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  8.18 (s, 1 H), 7.98 (s, 1 H), 7.93 (dd,  $J = 8.8, 1.6$  Hz, 1 H), 7.77 (d,  $J = 9.2$  Hz, 1 H), 7.73 (dd,  $J = 8.0, 1.6$  Hz, 1 H), 7.09 (d,  $J = 8.4$  Hz, 1 H), 3.93 (s, 3 H), 3.49 (s, 2 H), 2.58 (br s, 8 H), 2.33 (s, 3 H); MS (EI)  $m/z$  381 ( $M^+ + 1$ ).

15    **Example 136**

**2-Hydroxy-3-[5-(4-methyl-piperazin-1-ylmethyl)-pyridin-2-yl]-1H-indole-5-carboxylic acid (thiophen-2-ylmethyl)-amide dihydrochloride**

The title compound was prepared as described for Example 67 using 2-hydroxy-3-[5-(4-methyl-piperazin-1-ylmethyl)-pyridin-2-yl]-1H-indole-5-carboxylic acid methyl ester

20    (0.057 g, 0.15 mmol) and 2-(aminomethyl)-thiophene (0.042 g, 0.38 mmol) as starting materials. The base was obtained as an orange yellow solid (0.032 g, 46% yield), which was transformed to the orange yellow dihydrochloride (0.026 g, 70% yield):  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  8.27 (s, 1 H), 8.16 (d,  $J = 1.2$  Hz, 1 H), 8.11 (dd,  $J = 8.8, 1.6$  Hz, 1 H), 8.03 (d,  $J = 9.2$  Hz, 1 H), 7.64 (dd,  $J = 8.0, 1.6$  Hz, 1 H), 7.31 (dd,  $J = 5.2, 1.6$  Hz, 1 H), 7.18 (d,  $J = 8.4$  Hz, 1 H), 7.08 (dd,  $J = 3.6, 1.2$  Hz, 1 H), 6.98 (dd,  $J = 5.2, 3.6$  Hz, 1 H), 4.80 (s, 2 H), 4.24 (s, 2 H), 3.6 (br s, 8 H), 3.02 (s, 3 H); MS (EI)  $m/z$  462 ( $M^+ + 1$ ).

**Example 137**

30    **2-Hydroxy-3-[5-(4-methyl-piperazin-1-ylmethyl)-pyridin-2-yl]-1H-indole-5-carboxylic acid benzylamide dihydrochloride**

The title compound was prepared as described for Example 67 using 2-hydroxy-3-[5-(4-methyl-piperazin-1-ylmethyl)-pyridin-2-yl]-1H-indole-5-carboxylic acid methyl ester and benzylamine (0.041 g, 0.38 mmol). The base was obtained as an orange yellow oil (0.030

g, 44% yield), which was transformed to the orange yellow dihydrochloride (0.029 g, 83% yield):  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  8.27 (s, 1 H), 8.19 (d,  $J = 0.8$  Hz, 1 H), 8.09 (dd,  $J = 9.2, 2.0$  Hz, 1 H), 8.03 (d,  $J = 9.2$  Hz, 1 H), 7.67 (dd,  $J = 8.0, 1.6$  Hz, 1 H), 7.48 (s, 1 H), 7.43 (d,  $J = 7.6$  Hz, 1 H), 7.36 (t,  $J = 7.2$  Hz, 2 H), 7.28 (d,  $J = 7.2$  Hz, 1 H), 7.19 (d,  $J =$   
5 8.4 Hz, 1 H), 4.66 (s, 2 H), 4.16 (s, 2 H), 3.6 (bs, 8 H), 3.02 (s, 3 H); MS (EI)  $m/z$  456 ( $\text{M}^+ + 1$ ).

### Example 138

#### 10 3-(5-Diethylaminomethyl-pyridin-2-yl)-2-hydroxy-1H-indole-5-carboxylic acid (2-methanesulfonyl-ethyl)-amide hydrochloride

The title compound was prepared as described for Example 67 using methyl 3-{5-[(diethylamino)methyl]pyridin-2-yl}-2-hydroxy-1H-indole-5-carboxylate (0.071 g, 0.2 mmol) and (2-aminoethyl)methylsulfone hydrochloride (0.080 g, 0.5 mmol) as starting  
15 materials. The base was obtained after preparative HPLC purification (XTerra<sup>®</sup> PrepMS C<sub>8</sub> columns 10  $\mu\text{m}$ , 19x300mm; 0.1 M  $\text{NH}_4\text{OAc}$  buffer/acetonitrile, from 90:10 to 40:60, as eluent gradient) as an orange yellow solid (0.030 g, 34% yield), which was transformed to the yellow hydrochloride salt (0.023 g, 72% yield):  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ , 400 MHz)  $\delta$  8.21 (s, 1 H), 8.11 (s, 1 H), 7.95 (s, 2 H), 7.60 (dd,  $J = 8.0, 1.2$  Hz, 1 H), 7.14 (d,  $J = 8.0$  Hz, 1 H),  
20 4.35 (s, 2 H), 3.93 (t,  $J = 6.4$  Hz, 2 H), 3.51 (t,  $J = 6.4$  Hz, 2 H), 3.29 (m, 4 H), 3.09 (s, 3 H), 1.43 (t,  $J = 7.2$  Hz, 6 H); MS (EI)  $m/z$  445 ( $\text{M}^+ + 1$ ).

### Pharmaceutical compositions

25 According to one aspect of the present invention there is provided a pharmaceutical composition comprising a compound of formula **Ia** or **Ib**, as a free base or a pharmaceutically acceptable salt, solvate or solvate of salt thereof, for use in the prevention and/or treatment of conditions associated with glycogen synthase kinase-3.

30 The composition may be in a form suitable for oral administration, for example as a tablet, for parenteral injection as a sterile solution or suspension. In general the above compositions may be prepared in a conventional manner using pharmaceutically carriers or

diluents. Suitable daily doses of the compounds of formula **Ia** or **Ib** in the treatment of a mammal, including man, are approximately 0.01 to 250 mg/kg bodyweight at peroral administration and about 0.001 to 250 mg/kg bodyweight at parenteral administration. The typical daily dose of the active ingredients varies within a wide range and will depend on various factors such as the relevant indication, the route of administration, the age, weight and sex of the patient and may be determined by a physician.

A compound of formula **Ia** or **Ib**, or a salt thereof, can be used on its own but will usually be administered in the form of a pharmaceutical composition in which the formula **Ia** or **Ib** compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable diluent or carrier. Dependent on the mode of administration, the pharmaceutical composition may comprise from 0.05 to 99 %w (per cent by weight), for example from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

A diluent or carrier includes water, aqueous polyethylene glycol, magnesium carbonate, magnesium stearate, talc, a sugar (such as lactose), pectin, dextrin, starch, tragacanth, microcrystalline cellulose, methyl cellulose, sodium carboxymethyl cellulose or cocoa butter.

A composition of the invention can be in tablet or injectable form. The tablet may additionally comprise a disintegrant and/or may be coated (for example with an enteric coating or coated with a coating agent such as hydroxypropyl methylcellulose).

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula **Ia** or **Ib**, or a pharmaceutically acceptable salt, solvate or solvate of salt thereof, a hereinbefore defined, with a pharmaceutically acceptable diluent or carrier.

An example of a pharmaceutical composition of the invention is an injectable solution containing a compound of the invention, or a pharmaceutically acceptable salt, solvate or solvate of salt thereof, as hereinbefore defined, and sterile water, and, if necessary, either

sodium hydroxide or hydrochloric acid to bring the pH of the final composition to about pH 5, and optionally a surfactant to aid dissolution.

Liquid solution comprising a compound of formula **Ia** or **Ib**, or a salt thereof, dissolved in  
5 water.

<u>Solution</u>	<u>mg/mL</u>
Compound X	5.0% w/v
Pure water	To 100%

#### Medical use

10 Surprisingly, it has been found that the compounds defined in the present invention, as a free base or a pharmaceutically acceptable salt, solvate or solvate of salt thereof, are well suited for inhibiting glycogen synthase kinase-3 (GSK3). Accordingly, the compounds of the present invention are expected to be useful in the prevention and/or treatment of conditions associated with glycogen synthase kinase-3 activity, i.e. the compounds may be  
15 used to produce an inhibitory effect of GSK3 in mammals, including man, in need of such prevention and/or treatment.

GSK3 is highly expressed in the central and peripheral nervous system and in other tissues. Thus, it is expected that compounds of the invention are well suited for the prevention  
20 and/or treatment of conditions associated with glycogen synthase kinase-3 in the central and peripheral nervous system. In particular, the compounds of the invention are expected to be suitable for prevention and/or treatment of conditions associated with especially, dementia, Alzheimer's Disease, Parkinson's Disease, Frontotemporal dementia Parkinson's Type, Parkinson dementia complex of Guam, HIV dementia, diseases with  
25 associated neurofibrillar tangle pathologies and dementia pugilistica.

Other conditions are selected from the group consisting of amyotrophic lateral sclerosis, corticobasal degeneration, Down syndrome, Huntington's Disease, postencephalatic parkinsonism, progressive supranuclear palsy, Pick's Disease, Niemann-Pick's Disease,

stroke, head trauma and other chronic neurodegenerative diseases, Bipolar Disease, affective disorders, depression, schizophrenia, cognitive disorders, hair loss and contraceptive medication.

5 Further conditions are selected from the group consisting predemented states, Mild Cognitive Impairment, Age-Associated Memory Impairment, Age-Related Cognitive Decline, Cognitive Impairment No Dementia, mild cognitive decline, mild neurocognitive decline, Late-Life Forgetfulness, memory impairment and cognitive impairment, vascular dementia, dementia with Lewy bodies and androgenetic alopecia.

10

One embodiment of the invention relates to the prevention and/or treatment of dementia and Alzheimer's Disease.

Another embodiment of the invention relates to the prevention and/or treatment of  
15 bone-related disorders.

The dose required for the therapeutic or preventive treatment of a particular disease will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated.

20

The present invention relates also to the use of a compound of formula Ia or Ib as defined hereinbefore, in the manufacture of a medicament for the prevention and/or treatment of conditions associated with glycogen synthase kinase-3.

25 In the context of the present specification, the term "therapy" also includes "prevention" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention also provides for a method of treatment and/or prevention of conditions  
30 associated with glycogen synthase kinase-3 comprising administering to a mammal, including man in need of such treatment and/or prevention a therapeutically effective amount of a compound of formula Ia or Ib, as hereinbefore defined.

**Non-medical use**

In addition to their use in therapeutic medicine, the compounds of formula Ia or Ib as a free base or a pharmaceutically acceptable salt thereof, are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of GSK3 related activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutics agents.

**Pharmacology****Determination of ATP competition in Scintillation Proximity GSK3 $\beta$  Assay.****GSK3 $\beta$  scintillation proximity assay.**

The competition experiments were carried out in duplicate with 10 different concentrations of the inhibitors in clear-bottom microtiter plates (Wallac, Finland). A biotinylated peptide substrate, Biotin-Ala-Ala-Glu-Glu-Leu-Asp-Ser-Arg-Ala-Gly-Ser(PO<sub>3</sub>H<sub>2</sub>)-Pro-Gln-Leu (AstraZeneca, Lund), was added at a final concentration of 1  $\mu$ M in an assay buffer containing 1 mU recombinant human GSK3 $\beta$  (Dundee University, UK), 12 mM morpholinepropanesulfonic acid (MOPS), pH 7.0, 0.3 mM EDTA, 0.01%  $\beta$ -mercaptoethanol, 0.004 % Brij 35 (a natural detergent), 0.5 % glycerol and 0.5  $\mu$ g BSA/25  $\mu$ l. The reaction was initiated by the addition of 0.04  $\mu$ Ci [ $\gamma$ -<sup>33</sup>P]ATP (Amersham, UK) and unlabelled ATP at a final concentration of 1  $\mu$ M and assay volume of 25  $\mu$ l. After incubation for 20 minutes at room temperature, each reaction was terminated by the addition of 25  $\mu$ l stop solution containing 5 mM EDTA, 50  $\mu$ M ATP, 0.1 % Triton X-100 and 0.25 mg streptavidin coated Scintillation Proximity Assay (SPA) beads (Amersham, UK). After 6 hours the radioactivity was determined in a liquid scintillation counter (1450 MicroBeta Trilux, Wallac). The inhibition curves were analysed by non-linear regression using GraphPad Prism, USA. The K<sub>m</sub> value of ATP for GSK3 $\beta$ , used to calculate the inhibition constants (K<sub>i</sub>) of the various compounds, was 20  $\mu$ M.

The following abbreviations have been used:

MOPS	Morpholinepropanesulfonic acid
EDTA	Ethylenediaminetetraacetic acid
BSA	Bovin Serum Albumin

ATP      Adenosine Triphosphate  
SPA      Scintillation Proximity Assay  
GSK3      Glycogen synthase kinase 3

*Results*

- 5    Typical  $K_i$  values for the compounds of the present invention are in the range of about 0.001 to about 10,000 nM. Other values for  $K_i$  are in the range of about 0.001 to about 300 nM.